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EDITORIAL

PROGRESS IN HYPOTHERMIA

IN this issue of the Journal we present reviews of current knowledge about hypothermia.

Many developments in anaesthesia have come by accident; others, like hypothermia, have been the result of much careful and painstaking effort, first in the laboratory in animals, and then in man for whom this procedure is now invaluable for certain operations.

Hypothermia was originally confused with "artificial hibernation"—an inept phrase, because man does not hibernate—and little distinction was made between a state produced by cooling and that resulting from the use of the "lytic cocktail." If the circulation has to be interrupted for an appreciable period, the choice must lie between hypothermia or the establishment of an extracorporeal circulation.

The ultimate balance in the indications for these two techniques cannot at present be foreseen. Although hypothermia can prolong the safe period of circulatory arrest up to 10 minutes, this is insufficient to allow for the repair of some of the worst kinds of cardiac defects. "Deep" hypothermia in man may become possible and if its inherent dangers can be controlled, the time available would be extended. Present work at the Westminster Hospital suggests that this may be practicable. The Westminster team, by separately cooling the blood flowing to the left and right sides of the heart and returning it through cannulae in the pulmonary artery and the femoral artery respectively (*Brit. med. J.*, 1959, **1**, 565), have relieved most of the strain on the heart during cooling. With this technique they have successfully achieved temperatures around 15°C in human patients which apparently allowed complete circulatory occlusion for at least 45 minutes.

In neurosurgery good operating conditions can be obtained with hypothermia, particularly for the surgery of aneurysms, but it remains to be shown whether some of the current techniques of anaesthesia, like those with controlled respiration, are not preferable with greater economy of effort. The extracorporeal technique is at present more difficult but our ability to manage it grows, and the September issue of the Journal will contain a symposium devoted to this subject.

Hypothermia seems likely to remain the method of choice for patients requiring operations for coarctation of the aorta, and for those with uncontrollable katabolic activity.

Hypothermia is yet another of those fields which have opened up in the last few years, where progress has been made by the co-operative efforts of anaesthetist, surgeon and laboratory worker. No doubt the manner of its development will continue to provide the pattern for further advances in medicine.

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PHYSIOLOGY OF HYPOTHERMIA

BY

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PHYSIOLOGICAL responses to large falls in body temperature began to receive attention in the latter part of the 18th century. James Currie of Liverpool (1798) was prompted to examine the consequences to shipwrecked mariners of prolonged immersion in sea water. He was probably the first to notice the "after drop" in body temperature which occurs when cooling is stopped, and the further fall in body temperature which happens when a peripheral vasodilatation is evoked in a chilled man.

Further observations on the effects of body cooling on small animals were made during the 19th and early 20th centuries by Claude Bernard (1876), Walther (1862), Horvath (1881), Lefèvre (1911) and others. From their studies emerged the fact that small hibernating mammals could be cooled to near 0°C and rewarmed with survival, whereas the non-hibernators died at about 20°C. Smith and Fay (1940) tried to treat malignant disease by cooling patients to between 24 and 30°C. Although this treatment yielded no results as far as the diseases were concerned, a number of the dangers of the procedure became apparent. Their work led to further research in the technique of body cooling, so that it could be used as an adjunct to surgery in man. Following the work of Bigelow et al. (1950a), hypothermia has played an important role, particularly in the surgery of the heart, the great blood vessels and the brain.

This article deals with some of the physiological consequences of body cooling, culled from the literature and selected as being of practical interest to anaesthetists. It does not attempt to cover the vast number of papers on the subject, or to resolve differences of view on controversial issues.

It is clear, however, that the cooled patient must to some extent be regarded as a different organism from the ordinarily anaesthetized man, and that in his management a number of new rules apply.

Temperature measurement.

The idea that a temperature measurement in the mouth or rectum provides an adequate index of the temperature in other body sites has become ingrained in medical thought. Under steady state conditions, this assumption may be true, but during the rapidly changing conditions of cooling and rewarming, it has no validity. In the latter circumstances, the correct temperature of any one organ can only be determined by a recording device inserted into that structure. This is, however, in the case of such organs as the heart, brain, kidneys or liver, impracticable or dangerous. If it can be assumed that the temperature of the blood leaving the heart will bear a relationship to the temperature of these deep structures, then the most reliable index of aortic blood temperature is required. There is ample evidence that in man and animals, the oesophageal temperature at heart level is the most reliable index of heart and blood temperature under rapidly altering conditions (Cooper and Kenyon, 1957; Severinghaus, 1956). The temperature of the rectum during cooling and rewarming is a poor guide to that of the heart and other internal structures and may lag behind the heart temperature by as much as 3°C. Perhaps some of the differences of opinion as to the linearity or otherwise of various physiological changes with respect to temperature could be resolved if account were taken of the internal temperature variations in hypothermia.

The conditions which obtain when an organ is exposed for surgery render accurate assessment of its temperature very difficult. With an evaporating surface exposed to operating theatre air and an

internal core at the blood temperature, it would be illogical to ascribe any one temperature to the organ. The possible effects of the temperature gradients, for example, through the heart, in establishing an electrotonic current sufficient to cause abnormal excitation should be borne in mind.

A suitably calibrated thermocouple or thermistor device can be obtained commercially or be made in any laboratory, which, inserted into the oesophagus at heart level, would provide the most useful temperature index for those performing the cooling or rewarming of patients. Universal adoption of such a site for temperature measurement is desirable if only to enable future observations during hypothermia to be comparable.

Metabolism.

The whole body oxygen consumption falls as the body temperature is lowered in all mammalian species (Bigelow et al., 1950b; Woodruff, 1941; Adolph, 1950; Lynn et al., 1954). This is also true of the separate organs and the data on them is discussed elsewhere in this article. There has been much discussion as to whether the fall in oxygen consumption is a linear or exponential function of the body temperature. The arguments are usually based on a relationship between oxygen usage and the measurement of a temperature at a single so-called representative body site. The real solution to this problem awaits the determination of accurate "mean" body temperatures which as yet are not susceptible to precise measurement. On the data of Spurr et al. (1954) and Horvath et al. (1953), who found an exponential relationship, a Q_{10} of 2.3 is given for oxygen consumption. This agrees with the van't Hoff relationship determined for changes in temperature on exposure to conditions other than hypothermia.

The transport of oxygen to the tissues and its utilization will depend on the adequacy of pulmonary ventilation, the transfer of oxygen across the lung capillaries, the dissociation of oxyhaemoglobin, an adequate capillary circulation in the tissues, the tissue oxygen pressures (pO_2), and the adequate functioning of the oxidative enzymes in the tissues.

Under the conditions of surgical hypothermia, with spontaneous breathing or with artificial respiration, the transfer of oxygen to the blood is accomplished satisfactorily (Dill and Forbes, 1941; Rosenhain and Penrod, 1951; Albers et al., 1958). The blood flow to vital structures (discussed under separate headings) is reduced, but remains adequate for gas transport to the tissues.

On cooling blood *in vitro*, there is a shift of the oxygen dissociation curve to the left, which means that haemoglobin will only give up its oxygen at tissue oxygen pressures which are considerably lower than usual (Brown and Hill, 1923). The tissue pO_2, estimated by analysis of venous blood or by the pO_2 of gas bubbles equilibrated in the body cavities and subcutaneously, was found to be lowered as expected from the shift in the oxygen dissociation curve (Adolph, 1956). The tissue oxygen requirement is reduced in hypothermia. Further measurements on the dog by Albers et al. (1958), in which the animal was subjected to a low pO_2 in the inspired air (17 mm Hg), did not demonstrate any difference in the lethal temperature. Their work showed that tissue anoxia was unlikely to be the cause of death in hypothermia. Little evidence has yet been produced to support the hypothesis that the enzyme processes involved in tissue utilization of oxygen are inactivated by surgical hypothermia.

The whole body respiratory quotient falls markedly with cooling (Bickford and Mottram, 1958; Usinger, 1957), with a partial recovery after 1 to 3 hours. Interpretation of changes in respiratory quotient, in the presence of a changing CO_2 solubility and the effects of various anaesthetic agents on respiratory function, is difficult. Gray et al. (1956) cooled the isolated perfused rabbit liver and found that both O_2 consumption and CO_2 production fell. The respiratory quotient at 24°C was about 0.80–0.87, which was not greatly different from that at 37°C after the perfusion had run for 1–2 hours. It was thought that the liver could utilize carbohydrate at 24°C.

Studies on man undergoing vascular surgery with hypothermia have demonstrated a failure to utilize injected glucose at body temperatures of about 30°C and below (Wynn, 1954). Fructose injected intravenously disappears from the circulating blood and concomitantly the blood glucose level rises. Wynn (1956) concluded that glucose was unable to enter cells under the conditions of surgical hypothermia, and that glucose formed within cells could not be metabolized but could

leak out, whereas fructose could enter cells and be converted to glucose which then subsequently reappeared in the extracellular fluid.

Respiration.

The adequacy of spontaneous breathing during hypothermia is differently reported in the literature and much of the argument seems to be referable to the type and amount of anaesthetic used.

With the reduction in body temperature, there is usually a drop in the pH of arterial blood (Hegnauer and Penrod, 1950; Swan et al., 1953). The origin of this acidosis is a matter for considerable discussion. The solubility of CO_2 in blood is increased as the temperature falls. Cranston et al. (1955) reported that, in dogs under hypothermia, the body tended to maintain a steady arterial blood pCO_2, although the concentration of dissolved CO_2 rose considerably. This was not a function of a failing respiratory centre because there was a normal respiratory response to the inhalation of 6 per cent CO_2. These experiments would suggest that during cooling there is a respiratory acidosis as a result of the increased solubility of CO_2.

Brewin et al. (1955) found a respiratory acidosis in dogs when the animals breathed spontaneously during hypothermia, but he disagreed with the hypothesis that this could be ascribed solely to the increased solubility of CO_2. By comparing the pCO_2/pH plot of blood from a hypothermic dog with that of blood taken from the same dog prior to cooling, they found evidence that a metabolic acidosis also occurs. This was usually present and was equivalent to a decrease in CO_2 combining power of about 5 ml/100 ml at a pCO_2 of 40 mm Hg. After rewarming, the metabolic acidosis was moderate, but if a 10-minute period of circulatory arrest had occurred during hypothermia, the metabolic acidosis was much greater. During hypothermia, the blood lactate concentration was raised by 1–2 m.equiv/l., and if circulatory arrest was carried out for a 10-minute period, the lactate level in the blood subsequently rose much higher.

When artificial respiration is carried out with sufficient vigour to reduce the alveolar and arterial CO_2 tensions, the arterial pH can be kept up to a normal level (Swan et al., 1953).

Another change produced on the respiratory system by hypothermia is a considerable increase in the anatomical and physiological deadspaces (Severinghaus, et al., 1957), which is thought to be due to bronchodilatation. This does not seem to cause any difficulty, however, in elimination of CO_2.

Endocrine disturbances.

Provided the anaesthesia is sufficiently deep to suppress shivering, the activity of the thyroid gland is markedly reduced by body cooling (Fontaine and Lachiver, 1955). Antidiuretic hormone release from the pituitary is also depressed. The adrenal corticosteroid output and adrenaline and noradrenaline secretion are reduced during hypothermia. The adrenal vein blood studies of Egdahl et al. (1955) indicated that the 17-hydroxycorticosteroid secretion was greatly reduced at low body temperature. This depression also occurs if the adrenal gland is cooled with the rest of the animal at normal body temperatures (Egdahl et al., 1955). The adrenal response to injected ACTH is lowered in hypothermia as assessed by adrenal ascorbic acid depletion (Khalil, 1954), or the consequent secretion of 17-hydroxycorticosteroids (Hume, et al., 1956). The pituitary ACTH secretion is also reduced in hypothermia. On rewarming, these endocrine functions are re-established, though there is some discussion as to whether the adrenal corticosteroid output is less after surgery under hypothermia than after the same operation at normal temperatures.

There is evidence that in dogs, after hypothermia lasting 3 days during which surgery was performed, the adrenal 17-hydroxycorticosteroid output in the urine rises to higher levels on rewarming than it does in dogs who are anaesthetized but not cooled (MacPhee et al., 1958). In these experiments there was no marked reduction in corticosteroid output during hypothermia.

Endogenous production of insulin is reduced at low body temperatures (Fuhrman and Crismon, 1947; Horvath and Spurr, 1956). The action of insulin in reducing blood sugar varies according to the species studied and the conditions under which the observations are made. It is safe to state that this function is reduced. In man, during surgical hypothermia, insulin did not reduce the blood sugar level which was raised following an intravenous infusion of glucose (Wynn, 1954).

Heart and circulation.

As the body cools, the heart rate falls, so that it is about halved at a body temperature of 25°C. This slowing appears to be a consequence of cooling the pacemaker, rather than to extrinsic factors (Prec et al., 1949). The utilization of oxygen is reduced by 50 per cent at a heart temperature of 25°C as compared with that at 37°C. This implies a higher relative oxygen consumption by the heart in hypothermia as contrasted with most other tissues.

Coronary blood flow falls by approximately 45–50 per cent as the temperature is reduced from 37–26°C. There is evidence that in hypothermia, provided the heart is beating normally, the supply of oxygen to the heart muscle is adequate to meet its calculated requirements (Penrod, 1951; Hegnauer and D'Amato, 1954). The elimination of CO_2 also appears to occur without difficulty.

Cardiac output falls provided shivering does not occur and various reports are given in the literature of the changes in stroke volume. An important study on dogs by Brendel (1957) in Thauer's laboratory draws attention to the relationship between stroke volume at differing levels of anaesthesia and the development of cardiac arrest. Their data fell into three groups, one in which the anaesthesia was light, when the stroke volume increased as the temperature fell from 30 to 20°C, and these dogs died with ventricular fibrillation. A second group under deep narcosis had, between these two temperatures, a fall in stroke volume and died in asystole. The third group at an intermediate level of anaesthesia had little or no change in stroke volume, survived longer and the ultimate cause of death was not known. Although the minute volumes fell, the stroke volume appeared to increase if the body oxygen consumption remained high, and to decrease if the oxygen was kept low by deeper narcosis.

Changes occur in the electrocardiogram including prolongation of the P–R interval and lengthening of the QRS complex. Elevation of the S–T segment or the appearance of a wave (Bigelow et al., 1950a; Osborn, 1953) rising steeply from the S wave is said to herald the onset of ventricular fibrillation. The factors determining these changes in the S–T segment are not clearly understood. A similar wave can be produced at normal body temperature by breathing high concentrations of CO_2, and it disappears on reverting to breathing room air (Altschule and Sulzbach, 1947).

The bradycardia which occurs during hypothermia in dogs is accompanied by a prolongation of systole and isometric contraction. This occurs to a greater extent than when the heart is slowed by a vagal stimulation at normal temperatures (D'Amato, 1956).

The work done by the heart per minute is reduced by cooling to about a tenth of normal, whereas the work per stroke is only reduced by about a half.

The origin of ventricular fibrillation, when it occurs in hypothermia, is influenced by a number of factors. The type of anaesthetic plays a part; and of the barbiturates, thiopentone seems the least likely to cause fibrillation (Covino et al., 1954). Mechanical stimulation of the heart by such means as catheters in the ventricle or surgical procedures help to induce ventricular fibrillation (Hegnauer et al., 1951). Underventilation of the lungs with the consequent rise in CO_2 content in the blood, with a fall in blood pH, predispose the heart to ventricular fibrillation. Swan et al. (1953) have drawn attention to the need for adequate pulmonary ventilation in the prevention of ventricular fibrillation. Abrupt falls in systemic arterial pressure, with presumably a sharp drop in coronary blood flow, can precipitate the onset of fibrillation. The ionic equilibrium in the blood plays a part in the initiation of cardiac arrhythmias during hypothermia, and the relative concentrations of potassium and calcium are particularly important (McMillan et al., 1955). There is some evidence that depriving the heart of its sympathetic nerves affords protection against ventricular fibrillation (Shumacker et al., 1956).

The blood flow in the brain, kidney and splanchnic area is reduced as the body temperature falls. In the dog, the femoral vascular bed dilates down to oesophageal temperatures of about 34°C and below this vasoconstriction occurs. Then at 28–25°C a second vasodilatation takes place which may be due to the direct action of cold on the blood vessels (Pappenheimer et al., 1948). The dilatation occurring at temperatures

in the region of 34°C depends on the activity of cholinergic sympathetic nerves (Covino and Beavers, 1957). In man, there is no evidence that the lower limb blood flow increases with cooling, and in fact the calf blood flow is reduced and the peripheral resistance in the region remains steady or increases slightly (Kenyon and Cooper, 1956b).

One of the most common uses of hypothermia is in circumstances which require the aorta to be clamped for a considerable time. At normal body temperatures, arrest of the circulation is followed by a reactive hyperaemia distal to the site of occlusion. This hyperaemia is only reduced by cooling when the circulatory arrest lasts a short while. After occlusions lasting more than 30 minutes, the vasodilatation which follows re-establishment of the circulation is large and lasts as long when the body is cold as when it is warm. Under these conditions, hypothermia affords no protection from the pooling of a considerable volume of blood distal to the site of circulatory arrest (Kenyon and Cooper, 1956a, b). It may be, of course, that tissues distal to an arterial occlusion fall to similar temperatures, whether or not generalized body cooling has previously been carried out, provided the period of absent blood supply is sufficient.

Nervous system.

A fall in body and brain temperature results in a decrease in cerebral oxygen consumption. In dogs, at 25°C the oxygen uptake by the brain is about one-third of that which occurs at 37°C (Bigelow et al., 1950b; Rosomoff and Holaday, 1954). Over this range, the oxygen consumption is a linear function of temperature (Rosomoff and Holaday, 1954; Kleinerman and Hopkins, 1955). This latter observation is true also of rat cerebral cortex slices studied *in vitro* with the Warburg apparatus. A concurrent fall in brain blood flow occurs during cooling. This decrease parallels the change in oxygen consumption, and the rate of reduction of cerebral blood flow was found by Rosomoff and Holaday (1954) to be 6.7 per cent per °C change in temperature. In their experiments the mean arterial pressure was reduced by only 4.8 per cent per °C. This implied a rise in the resistance to flow through the brain blood vessels, and that at 25°C there was a two- or threefold increase in cerebral vascular resistance. In the presence of a varying mean arterial blood pressure, a constancy of flow was maintained at a given temperature. This could only occur if an active mechanism were present, tending to maintain a fixed flow in the presence of a fluctuating arterial pressure. It was suggested that the regulating mechanism was a function of the respiratory blood gas tensions. Kleinerman (1956) has demonstrated that during hypothermia in dogs and monkeys, a rise in alveolar CO_2 tension initiates a vasodilatation in the brain.

Cerebrospinal fluid pressure falls as the body temperature is lowered, except when shivering takes place. This latter occurrence elevates the c.s.f. pressure. The fall in c.s.f. pressure is paralleled by a reduction in venous pressure, and Rosomoff and Gilbert (1955) estimated the change to be about 5.5 per cent per °C. He also found that with falling temperature there was a shrinkage of the brain substance at 25°C of 4.1 per cent, and an increase in the intracranial space not occupied by brain of 31.8 per cent. The brain as it contracts becomes firmer and this may, to some extent, simplify its handling during surgery.

The electroencephalogram begins to change as the body temperature falls to between 36–32°C. A decrease occurs in the amplitude of the potentials beginning in the occipital and parietal areas and later in the frontal regions. Large amplitude delta waves appear, particularly in the frontal area, at about 30°C. The electrical activity measured with the e.e.g. then declines until, between 18–20°C, no potentials can be recorded.

The respiratory centre in dogs was found by Cranston et al. (1955) to react in a normal fashion when the animals inhaled 6 per cent CO_2 in air at body temperatures of 25–27°C. Increases in respiratory minute volume so evoked did not differ significantly between cooled dogs and those at normal body temperature.

The level of temperature at which cortical function is sufficiently impaired to cause loss of consciousness has been variously recorded in the literature. During rewarming, patients have been capable of rational conversation at body temperatures as low as 29°C, and when the body temperature returned to normal, retained a clear memory of the events which happened at the start of rewarming (Cooper and Kenyon, 1957). Observations on the loss of consciousness and retrograde

amnesia during hypothermia show a wide variation and are often difficult to interpret because of the differences in circulating anaesthetic or narcotic agents.

One disturbing response of cooling on the central nervous system is a lowering of the threshold for the initiation of epileptiform convulsions (Noell et al., 1952), particularly at temperatures below 30°C. Both electrical stimulation and metrazol in what would normally be sub-threshold amounts cause convulsive reactions to occur during hypothermia.

Afferent nerves have a higher threshold to stimulation at 25°C, but the action potentials evoked are greatly increased in amplitude and duration. The afferent volleys are poorly synchronized and act more like a tetanus. These two effects of cooling lead to an enhanced central response to afferent stimulation (Brooks et al., 1955). Further, there is a tendency for certain afferent stimuli, which at ordinary body temperatures evoke pure monosynaptic responses, to spread to other pathways giving rise to reflexes with polysynaptic components (Koizumi et al., 1954). Although, therefore, the afferent fibres may be less readily stimulated, the central response which follows their firing may be more vigorous and widespread than in the warm animal.

It has been suggested that such a polysynaptic discharge down the autonomic nerves to the heart may occur, during hypothermia, as a result of visceral stimulation in surgery, and that the central "spill over" can be in part avoided by an adequate depth of anaesthesia.

A matter of major importance is the degree of protection afforded to nervous tissue from the effects of circulatory arrest by hypothermia. Extension of the safe period of arrest of the brain circulation from 3 minutes at 37°C to 15 minutes at a body temperature of 25°C has been reported (Lougheed and Kahn, 1955). The time of 15 minutes seems to be the maximum permissible. The spinal cord is also endangered by prolonged occlusion of its circulation. A considerable incidence of paraplegic symptoms could be expected to follow a 1-hour period of clamping the thoracic aorta, and this incidence would be reduced by cooling the cord to below 30°C (Beattie et al., 1953).

There is no striking evidence that cooling to 25–30°C *per se* produces any permanent defect in memory, intelligence or other psychological functions.

A remarkable series of experiments by Rosomoff (1955), on dogs, demonstrated a high degree of protection from cerebral infarction after ligation of the middle cerebral artery when the operation was performed at body temperatures of 22–24°C.

Renal function and body water.

Studies have been made on the water and sodium excretion in dogs and rats (Moyer et al., 1956; Andjus and Morel, 1952) via the kidney and on the glomerular filtration rate, renal blood flow and potassium excretion in dogs. The glomerular filtration was estimated by creatinine clearance and the renal plasma flow by para-amino hippurate clearance. In these experiments, there was no change in haematocrit values. As the body temperature fell, there was a drop in mean blood pressure (to 90 per cent of control at 30°C and 75 per cent of control at 25–27°C). The glomerular filtration rate and the renal blood flow both dropped to 31 per cent and 28 per cent of control values, respectively, at 25–27°C. Despite this, there was no concurrent fall in sodium excretion or urine volume. This state of affairs was not altered by maintaining the blood pressure at control levels with noradrenaline or by prolonging the hypothermia. Potassium excretion also fell to 63 per cent of the control amount at 25–27°C. It was suggested that tubular reabsorption is defective in hypothermia and that the enzymatic processes responsible for reabsorptive and secretory mechanisms are depressed, though further experimental proof is still needed.

Although some protection is afforded to the kidney against the effects of complete occlusion of its blood supply, there is some residual damage which depends on the length of time of anoxia. A low pressure trickle of blood through the organ, such as can flow via the lumbar collaterals, helps to prevent the damage. There is some evidence of lipoid accumulation in the distal tubules due to cooling alone (Knocker, 1955).

There have been varying reports on the division of body water between the circulating blood and the extra- and intracellular compartments during hypothermia. If shivering occurs, there may be a

shift of water from the interstitial compartment into the skeletal muscle cells (D'Amato, 1954). During this phase, there may be a shift of water out of the plasma into the interstitial regions, and the increased haematocrit sometimes observed may also represent an addition of cells to the blood from the spleen. This latter possibility, from experiments on splenectomized dogs, seems unlikely (Ross, 1954). At lower temperatures without shivering, there is some reversal of these water shifts. There is also a tendency to lose some of the blood volume by pooling or sequestration in regions of low blood flow.

The occasional occurrence of effusons into body cavities, or of pulmonary oedema, has been reported (Walther, 1862; Woodruff, 1941), and more recently, in dogs during prolonged hypothermia, by MacPhee et al. (1958).

Deep hypothermia.

Following the publication of work by Andjus in 1951, in which adult rats had been resuscitated after cooling to 1°C, a good deal of attention has been paid to methods of body cooling down to near freezing. In small animal work, the creatures are cooled in closed containers, without any pharmacological adjuncts, down to body temperatures of 15–20°C (Andjus and Smith, 1955). They are therefore, during this stage of cooling, exposed to a diminishing atmospheric pO_2 and a rising pCO_2. They are then immersed in crushed ice and the body temperature reduced to between 0–1°C. At this time the heart has ceased to beat and respiration has stopped. Rewarming is carried out by heating the heart first, together with artificial respiration. The local heart heating is best accomplished with microwave diathermy. Using this technique, long-term survival was achieved in 80–100 per cent of rats, whose breathing and heart beats had ceased for 40–60 minutes (Andjus and Lovelock, 1955).

More recently, larger mammals have been cooled to body temperatures between 10° and 0°C. Niazi and Lewis (1957) have cooled dogs and monkeys to these temperatures and successfully resuscitated them. In their experiments, they considered that the critical factor in this achievement was a raised concentration of CO_2 in the inspired air during cooling. The same authors (Niazi and Lewis, 1958) have successfully cooled a patient to 9°C for surgery with successful rewarming.

Another approach to the problem of cooling the body to such an extent that the heart lies quiescent has been to bypass the heart with a mechanical pump-oxygenator. In this way, the heart does little work as it cools and is rewarmed. This technique has been used to cool dogs to deep body temperatures of 4–7°C with successful rewarming (Gollan et al., 1954, 1955; Kenyon and Ludbrook, 1957). The relative merits of this technique over that of Melrose et al. (1955), in which the heart is stopped by injecting potassium citrate into the coronary circulation with the rest of the body perfused with oxygenated blood, await evaluation in practice.

GENERAL OBSERVATIONS

Some of the physiological changes which accompany a reduction in body temperature have been discussed. A consequence of these occurences is, however, to cause some anaesthetic and surgical manoeuvres, which at normal body temperatures are not hazardous, to become unsafe when the temperature is in the region of 30°C or below. For example, if during the course of an operation a large blood transfusion is required to maintain the arterial blood pressure, the use of stored citrated blood can lead to serious trouble. Citrated blood, after a week or more in storage, has a pH of 6.4–6.8, and the potassium levels in the plasma may rise as high as 8 m. equiv/l. (Kenyon and Cooper, 1956a, b). The citrate content is high enough to inactivate a considerable amount of free calcium ions in the circulating blood and this, together with the high level of plasma potassium and the low pH, may readily precipitate cardiac arrest. The temperature at which a rapid infusion of blood is given may be of importance, for if it is too low, then the cold stream of blood arriving at the heart may lead to the development of ventricular fibrillation. The need for large transfusions, though sometimes necessary after severe bleeding, can be minimized if a careful blood balance is kept and steps are taken to reduce the effects of factors such as reactive hyperaemia in areas distal to large arterial occlusions (Kenyon and Cooper, 1956a, b).

It is sometimes the practice in surgery to use intravenous infusions of glucose saline. At body

temperatures of 30°C or below, this may also add to the danger of hypothermia. As Wynn (1956) has demonstrated, glucose utilization and its removal from the extracellular space are grossly impaired under these conditions. The consequence of a steadily mounting glucose level in the blood is a rise in plasma osmolarity and this in turn causes a shift of water into the extracellular spaces with a resulting undesirable disturbance of blood electrolytes.

Brewin et al. (1955) have drawn attention to the damage which may occur in the dog liver when its circulation is arrested under hypothermia. When the circulatory occlusion was performed for a short time in such a way that a marked rise in central venous pressure with hepatic venous congestion occurred, there was severe structural damage to the liver and loss of hepatic function. Added to these events, a marked metabolic acidosis in part related to liver damage also occurred. These ill effects could be obviated by lowering the central venous pressure during the period of liver anoxia, when the resultant damage became trivial.

The use of drugs during the period of cooling calls for some care. Morphine, for example, is detoxified by the liver very much more slowly at low liver temperatures than at normal temperatures. Half-life times for the loss of free morphine from the plasma are given by Gray et al. (1956) as 3.7 minutes at 37°C and 94 minutes at 24°C. Similar impairment in the removal of barbiturates by the liver has been observed. A number of workers have found a sharp rise in arterial pressure during rewarming when noradrenaline has been given at low body temperatures. The possibility arises that this drug may in part remain inert in the circulation to become active at a time during rewarming when a transitory hypertension is least desired. The danger also of recurarization during rewarming and its consequences on respiration are also well recognized.

It seems that for the maximal safety of the patient the use of hypothermia must include careful biochemical control at all stages of the operation, for the physiological events occurring during cooling are not revealed by simple observations on the patient, nor are they always detectable by the most astute clinical acumen. The most rigorous documentation of all procedures by the anaesthetist with careful pre-operative planning and repeated observations on such matters as electrolytes, pH and CO_2 levels are the only good safeguards.

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CLINICAL ASPECTS OF INDUCED HYPOTHERMIA

Methods of Production and Indications for its Use

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Hypothermia is now firmly established as a therapeutic measure in certain surgical and non-surgical conditions. Many claims have been made for its advantages since its first clinical application in this country over five years ago. Some of the original indications for hypothermia are now not receiving such wide support as formerly and more recently new indications have been considered. Techniques used in the production of hypothermia have also changed widely since its first introduction.

The purpose of this paper is not so much to review the progress that has been made during the past few years, as to consider the clinical aspects of hypothermia as practised today. The subject can be divided into two broad fields which will be discussed, as follows:

(*a*) techniques used for the production of hypothermia

(*b*) clinical applications of hypothermia.

The object of employing hypothermia is to reduce the metabolic requirements, either of a specific vital organ or the body as a whole. This is carried out by various means and most of these involve cooling the whole body, even though the desired reduction in metabolism may only apply to one or more organs.

TECHNIQUES USED TO PRODUCE HYPOTHERMIA

The four methods for producing hypothermia are:

(1) Body surface cooling.
(2) Direct cooling of the blood stream.
(3) Application of cold to body cavities.
(4) Selective cooling of organs.

With the exception of local refrigeration of limbs beyond an arterial tourniquet, even the last two methods result in generalized hypothermia, although the degree of temperature reduction may be more marked in a specific organ.

The production of hypothermia by some form of surface cooling is by far the most widely practised technique, having the advantage that it can be carried out by the minimum of staff with simple equipment. A discussion of this must, of necessity, occupy the major portion of this review. While a prerequisite to the successful induction of the hypothermic state by any method is the obtunding of the body's natural defence reaction to cold, this is of particular importance when surface cooling is used. Otherwise, attempts at reducing body temperature are likely to defeat their own purpose and cause an increase, rather than a decrease in cellular metabolism.

A detailed description of the body's reaction to cold is outside the scope of this publication and readers are referred to the book by Burton and Edholm (1955) which deals fully with the subject. Nevertheless, some of these effects must be discussed, as attention will have to be directed to the measures which can be adopted to overcome them.

THE REACTION TO COLD

Vasoconstriction. This is the primary delicate reaction of the body to cold. It is not entirely reflex in origin, because, as Burton and Edholm (1955) state, it still occurs in sympathectomized animals, indicating a direct action on the blood vessels; Wright (1953) incriminates stimulation of the adrenal medulla with secretion of adrenaline as a causative factor. Blood is diverted from the cold skin to the deeper layers of the body, thus insulating the main blood stream from the surface cooling agent. The efficacy of any method of body surface cooling therefore depends on maintaining a coincident vasodilatation of the blood vessels of

the skin and subcutaneous tissues. Pooling of cold blood is also in part responsible for the continued fall in body temperature when the cooling agent is removed, which is a feature of surface cooling. This cold blood is gradually released into the general circulation, especially if the skin vessels dilate on removal of the cold stimulus. Sellick (1957) and Gray (1958) have both stressed the importance of maintaining vasodilatation as a safeguard against frostbite.

Endocrine response. The endocrine glands help to maintain another fine adjustment of the body to falls in environmental temperature. Reflex release of adrenaline from the suprarenals, besides causing vasoconstriction, stimulates cellular metabolism, mobilizing liver glycogen and increasing heat production. An increase in circulating pituitary thyrotropin resulting in excessive thyroxine secretion is another response to cold. This stimulates neoglucogenesis and mobilization of liver glycogen, all of which tend to cause a greater heat production and maintenance of body temperature. Exposure to cold acts as a form of stress, resulting in reflex secretion of A.C.T.H. which in turn causes discharge of adrenal corticoids. All of these endocrine responses are obtunded with the general metabolic reduction which occurs at low temperatures.

Shivering. This is the coarse reaction of the body to external cold and is by far the most effective means of raising body temperature. It is brought about by an increase in the temperature gradient between body surface and body core, and its intensity is proportional to the size of this gradient. Muscle action potentials are observed immediately on exposure to cold, before any change has occurred in the central temperature, and conversely shivering is abolished within one minute of raising skin temperature, again without any appreciable rise in general body temperature. The rapidity of these changes has led Davis and Mayer (1955) to suggest that their mediation is exclusively neurological. These workers also state that correction of the surface to central temperature gradient is imperative in the abolition of shivering in deep hypothermia. It was found that when rats which had been cooled to 20–25°C were reheated by raising the skin temperature to 30–40°C, the animals continued to shiver until the central temperature was above 31°C. Above this temperature the normal response occurred.

Using electromyography, Davis and Mayer (1955) have shown that visible shivering is a late manifestation of muscle action potential activity. This activity occurs early on exposure to cold and increases in frequency and intensity until it is observed visually. Invisible shivering may be recognized during induction of hypothermia as a generalized muscular hypertonus.

The undesirable effects of shivering are many, the most important being a rise in body oxygen consumption. On thinking, in retrospect, of the work of Krogh (1916), it would seem that uncontrolled shivering was the explanation for the initial rise in oxygen consumption which he reported during the induction of hypothermia. Even with inadequately controlled shivering, as when the French technique of artificial hibernation and the "lytic cocktail" was in use, Dundee et al. (1953a) reported a 5–25 per cent increase in metabolism during hypothermia in man and Dundee, Scott and Mesham (1953b) found rises of 10–70 per cent in dogs. The importance of complete abolition of shivering is illustrated by these workers who recorded a fall in oxygen consumption of only 10 per cent in one shivering patient whose body temperature had been reduced 9.5°C below normal, as compared with falls of 40–70 per cent for patients at the same temperature who were not shivering.

Both pulse rate and arterial blood pressure often rise as the result of shivering. The rise in pulse rate is a valuable guide to its onset at low body temperatures, and in the absence of any other explanation for a rise, the imminent onset of shivering must be considered.

It cannot be stressed too often that the body's reaction to cold must be obtunded if cooling of the body core is to be successful. Furthermore, if hypometabolism is to be achieved, a violent stress response resulting in greatly increased metabolic rate and endocrine activity must be avoided.

From the practical point of view, two essentials are necessary for the induction of hypothermia by surface cooling.

(1) Adequate vasodilatation to ensure that the whole blood stream is subjected to the temperature of the body surface, thereby effecting cooling of the whole body.

(2) Complete abolition of shivering. Of all the responses to cold, shivering alone is capable of generating sufficient heat, or sufficiently increasing metabolism, to materially upset the course and object of hypothermia.

The methods which have been employed to meet these two requirements have overlapped to a certain extent. It is simpler, therefore, to consider the various adjuvants to the production of hypothermia by surface cooling under the different groups of drugs employed, rather than in relation to their specific actions.

ADJUVANT DRUGS

General anaesthesia. Deep general anaesthesia has been used by Bigelow et al. (1950) and is effective both in preventing shivering and producing vasodilatation. However, the associated metabolic depression and histotoxic effects of deep anaesthesia are undesirable and it is generally agreed that light anaesthesia, combined with a specific vasodilator drug and means of suppressing shivering, is more desirable. It is important to discuss the advantages of several of the most widely used anaesthetic agents.

Nitrous oxide-oxygen alone will provide adequate vasodilatation, provided the temperature of the cooling medium is not too low (10–20°C) (Clutton-Brock, 1958). Parkhouse (1957) has also described the value of nitrous oxide in preventing shivering. This is due to its analgesic potency. Nitrous oxide is often of value when chlorpromazine and analgesics alone have not proved sufficient. Ether is the most popular of the potent general anaesthetics used to produce vasodilatation (Virtue, 1955; Sellick, 1957). The latter prefers ether to the other volatile agents because it is least irritant to the cooling myocardium. Furthermore, it can be eliminated by hyperventilation when the desired temperature has been achieved, thus ensuring that during periods of cardiac arrest the tissues, and especially the brain, are relatively free from histotoxic drugs.

Recently Vandewater et al. (1958) and Campkin and Inglis (1958) have reported favourably on the use of light halothane anaesthesia in the production of hypothermia. The drug is not inflammable and appears to be particularly suitable for use in neurosurgery, because of its other properties. At concentrations of 0.5–1 per cent they found that respiratory depression was not a feature during induction of anaesthesia to temperatures of 29°C.

The most favoured form of general anaesthesia is nitrous oxide-oxygen, with or without thiopentone induction, combined with muscle relaxants (usually tubocurarine chloride) to suppress shivering. It is not inflammable, carries the minimum risk of histotoxic anoxia and recovery is prompt. However, its use is limited to operations where controlled respiration is permissible.

With any general anaesthetic technique, care should be taken to avoid undue falls in blood pressure, lest cooled blood be pooled in the dependent parts of the body. To this end Burrows et al. (1956) have suggested tipping the patient at frequent intervals. These considerations apply also to the other drugs which have been employed.

Ganglion-blocking drugs. While these produce adequate vasodilatation Dundee, Mesham and Scott (1954) found that, used alone, they did not prevent shivering and this largely counteracted their efficacy as adjuvants in the production of hypothermia. Eccleston et al. (1956) report favourably on the use of trimetaphan camphorsulphonate (Arfonad) and claim that, in addition to producing vasodilatation, it prevents shivering by an unknown mechanism, and protects the myocardium by reducing the load on the heart. The ganglion-blocking drug, azamethonium chloride (Pendiomid) has proved satisfactory in the hands of Ciocatto and Cattaneo (1956), both in experimental and clinical use. With doses of 0.25 mg/kg, which produce only a slight degree of hypotension, they claim that temperatures of 27°C can be reached after 45 minutes of surface cooling in conscious patients. Neither this claim, nor the advantages of rapid cooling have been substantiated by other workers.

Phenothiazines. Chlorpromazine, a constituent of the original French "lytic cocktail", has been shown by many workers (Dundee, Mesham and Scott, 1954; Ripstein, Freidgood and Solomon, 1954; Moyer et al., 1957) to be the most effective single drug in inducing hypothermia, and despite the introduction of allegedly less toxic substitutes, it still enjoys a considerable popularity. Its success is due to its vasodilatating action, its ability to suppress shivering and its

central sedative action which causes a state of tranquillity from which the undisturbed patient subsides into normal sleep. Vasodilatation results from its adrenolytic action (Dobkin et al., 1954), a local action on vessels and an effect on the vasomotor centres and sympathetic ganglia (Foster et al., 1954), while its direct depressant effect on muscles, as demonstrated by Burn (1954), probably explains its action in suppressing shivering. These desirable actions are enhanced when the drug is used in conjunction with general anaesthesia. It must be remembered that under these circumstances chlorpromazine potentiates the action of narcotics, analgesics, muscle relaxants and local analgesics (Courvoisier et al., 1953), otherwise undue and prolonged depression may result.

Undesirable hypotension and tachycardia may complicate chlorpromazine administration, particularly when large doses are used (Hellings, 1958). Thornton (1957) emphasizes the importance of this by advocating a test dose of 25 mg some days before operation, and modifying or even omitting the dosage used during the production of hypothermia, depending on the response to this test dose. These undesirable effects on blood pressure can be mitigated by the use of smaller doses; those of the order of 10–20 mg are usually sufficient to suppress shivering. Burrows et al. (1956), in their series of 50 patients, found 20–50 mg to be sufficient to achieve temperatures of 28–30°C. Rather than exceed these doses, and run the risk of hypotension, other less toxic adjuvant drugs should be used. The hypotension produced by chlorpromazine is all the more undesirable in that it does not respond fully to the commonly used vasopressors except phenylephrine and noradrenaline (Dundee, 1958).

Jaundice, a rare complication of chlorpromazine administration, has been reported by Sussman and Summer (1955) to occur with doses as low as 50 mg. Other reported undesirable side effects are agranulocytosis (Tasker, 1955), nonthrombocytopenic purpura (Marley, 1955), contact dermatitis, and irritation to the endothelium of veins in concentrated solutions.

Another phenothiazine derivative, promethazine, has frequently been used, either alone or in combination with chlorpromazine. It was also a constituent of the original "lytic cocktail". Promethazine possesses, to a lesser degree, many of the properties of chlorpromazine, but when used alone is much less effective in producing vasodilatation and suppressing shivering. It has a greater antihistamine activity than chlorpromazine, and one of the reasons for its use in hypothermic techniques, is its reputed ability to protect the body from the adverse effects of histamine release during both the induction of hypothermia and extensive surgical procedures. Other antihistamines, not belonging to the phenothiazine group, have been used by Ciocatto and Cattaneo (1956) for a similar reason.

Promethazine also has useful sedative properties and, like chlorpromazine, potentiates the action of most drugs used in general anaesthesia. Hypotension also follows its use in excessive doses, particularly in hypovolaemic subjects.

Recently Campkin and Inglis (1958) have reported on the value of promazine as an alternative to chlorpromazine. In small doses of about 20 mg this drug produces vasodilatation without severe falls in blood pressure or marked tachycardia.

Hydergine. This is a combination of three dehydrogenated alkaloids of ergot which possesses a profound vasodilator action. Hugenard (1956) substituted hydergine for chlorpromazine in an attempt to avoid the tachycardia so characteristic of the latter drug. Hydergine causes bradycardia, produces less clouding of consciousness and has fewer undesirable local effects than chlorpromazine.

Analgesic drugs. By increasing the threshold to sensory stimulation, the morphine-like analgesic drugs are effective in the prevention and suppression of shivering, and are valuable adjuvants to any hypothermic technique. It is interesting to note that Dundee, Mesham and Scott (1954) found that in a dog in which hypothermia had been induced with the aid of pethidine, there was a marked increase in the degree of shivering following the administration of nalorphine. Pethidine is commonly used as pre-operative medication before the induction of hypothermia and was also a constituent of the "lytic cocktail". It is also particularly valuable when general anaesthesia is not being used to aid cooling (Hunter, 1955). Levorphanol has also been used successfully by

Burrows et al. (1956) to abolish shivering during the rewarming period, its action being longer than that of pethidine. More recently Sedzimir and Dundee (1958) have commented on the value of mixtures of levorphanol and levallorphan in producing longstanding analgesia with minimal effects on respiration. Further work is needed to investigate the action on respiration of combinations of analgesic and antagonist drugs.

There is a great variety of effective drugs now available to aid in the production of hypothermia. The choice of a drug or combination of drugs must be dictated by the particular circumstances pertinent to the operative or other needs, and some of these drugs will be later considered.

TEMPERATURE CONTROL

Gray (1957) has recently emphasized the increasing control which the modern anaesthetist exerts over the vital systems of the anaesthetized patient. The induction of hypothermia by any method imposes added responsibilities in the control of temperature and the body's reaction to cooling.

The reduction in temperature which it is safe to impose is limited by the action of hypothermia on the heart. Ventricular fibrillation is the "temperature barrier" which has determined the lower limit beyond which it is unsafe to proceed. There is general agreement that the healthy human adult heart shows little tendency to ventricular fibrillation above 28°C (Ross, 1957). Between 28°C and 25°C the incidence of ventricular fibrillation rises steeply. The infant heart is more tolerant of hypothermia and Ross (1957) places the lower limit of safety at 26°C in these patients. In those with acquired heart disease (e.g. previous rheumatic disease) the liability to ventricular fibrillation is said to be increased; Bailey et al. (1954) consider that hypothermia is probably contra-indicated in such patients. Riley, Barila and Hughes (1956) have shown that other types of myocardial insufficiency increase the liability to fibrillation. Handling of the cold heart is also likely to produce ventricular fibrillation, and as will be seen later, the problem is more acute in cardiac than in other types of surgery.

To discuss the aetiology of hypothermic ventricular fibrillation in detail is outside the scope of this review. The problem must again be mentioned in connection with the complications of hypothermia and their treatment. Its importance is such that reliable means of measuring the temperature must be available to maintain the hypothermia within the safe limits as previously outlined.

Measurement of temperature. This is usually done by either the simple mercury or alcohol thermometers or by electrical thermocouples. Measurements of temperature in the rectum, nasopharynx, oesophagus, brain, muscle and heart have been made by various workers and the reliability of the various sites must be discussed. Lucas (1956) states that the commonly used rectal temperature gives little guide to the true temperature of the vital organs. Cooper and Kenyon (1957) have shown that this is particularly misleading if the thoracic aorta has been clamped. These latter workers have shown that during the cooling process the rectal temperature sometimes lagged 0.3–2.3°C behind the mid-oesophageal temperature at 30–33°C. Rectal temperature later fell to a lower level than oesophageal, and remained at a slightly lower level until rewarming was almost complete. Hellings (1958) has shown that rectal temperature also varies appreciably from that of the brain.

Mid-oesophageal readings are nearest to the temperatures of heart and brain and are the most reliable for clinical use. Severinghaus (1957) has described an ingenious apparatus for this purpose, called the telecor. This records the mid-oesophageal temperature, the electrocardiogram and serves as a stethoscope for heart and respiratory sounds. A record of skin temperature is also helpful, as a marked difference between this and body core indicates some degree of vasoconstriction, thus insulating the blood stream from the cooling agent.

TECHNIQUES OF COOLING

It is proposed under this heading to discuss the methods by which cold is applied to the body, rather than the anaesthetic and other drugs used in the techniques. The various drugs used have already been discussed in general and brief mention of some of these will be necessary from time to time. Some of the disadvantages and limitations of the various means by which the induction

of hypothermia is carried out will also be mentioned in this section.

Surface cooling. The application of a cooling agent to the body surface has been carried out in clinical practice in the following ways:

(1) Immersion in cold water.
(2) Application of ice packs.
(3) Contact with a special refrigerated blanket.
(4) Air cooling.

In some instances a combination of more than one method may be used in the same patient.

Immersion hypothermia. This has many exponents including Swan et al. (1953), Bigelow, Mustard and Evans (1954), Botterell et al. (1956, 1958), Sellick (1957) and Clutton-Brock (1958), and is the most rapid of the surface cooling techniques, as the cooling agent is more evenly distributed over the body surface. Most workers employ iced water at a temperature of 4–10°C. The patient is usually immersed in a bath and according to Lucas (1956) the water should be agitated frequently to prevent the formation of a warmer layer next to the skin. Sellick (1957) recommends frequent massage of the superficial tissues to prevent stagnation of blood and so speed up the heat exchange. He also suggests that the hands and feet should be lifted out of the water after a short time to prevent undue chilling of the digits. Clutton-Brock (1958) suggests that by keeping the water at a slightly higher temperature (10–20°C) the use of vasodilators other than nitrous oxide-oxygen is obviated. Even at this temperature cooling time is not prolonged provided the water is vigorously agitated by a pump.

Pask (1958) uses an interesting variation of immersion cooling by spraying iced water on the patient. The water drains into a collapsible bath and returns to the container from which it is again pumped over the patient. This method would appear to be very simple and cheap and produces almost as rapid cooling as immersion hypothermia.

Any form of immersion hypothermia results in rapid cooling; the technique is simple and the apparatus inexpensive, but the technique in adults is cumbersome; Bigelow, Mustard and Evans (1954) consider it to be aesthetically unattractive. A further disadvantage is that the technique cannot be easily carried out on the operating table and should ventricular fibrillation occur during cooling there would be considerable delay in performing a thoracotomy.

Vandewater et al. (1955; 1958) have described a special bath for the use of immersion hypothermia in neurosurgery. The head and neck of the patient are clear of the water and any preliminary preparation for craniotomy can be carried out during the cooling time. This is particularly useful when it is desirable to have a tape around the carotid arteries for temporary occlusion at a later date if needed. Since the operation can be carried out while the patient is still in the bath, this can be filled with warm water as required, and the drop in temperature accurately controlled, and the patient rewarmed to nearly a normal temperature by the end of the operation if this is required. In most of the other descriptions of immersion hypothermia, the body temperature is either allowed to return to normal spontaneously at the end of operation, or else the patient is placed on a refrigerating blanket the temperature of which is suitably raised.

Ice packs. The application of surface ice is the simplest method of surface cooling and has been reported by Gray (1955), Burrows et al. (1956) and Thornton (1957). Its simplicity makes it the method of choice in therapeutic hypothermia carried on in the wards and there are many reports of its use for this purpose (Rowbotham et al., 1957; Edwards, 1958; Johnston et al., 1958). Ice bags are placed all over the surface of the body, particularly over the left side of the chest, the axilla and groins, thus cooling the tissues in contact with the large blood vessels. Frequent changing of position of these bags is recommended. Thornton (1957) covers the ice packs with a wet sheet on to which he directs a stream of air from a fan to speed evaporation and hasten cooling. In therapeutic hypothermia where the main object is to counteract the tendency to hyperpyrexia the application of ice bags can be alternated with cold sponging as required (Sedzimir, 1956).

With this method rapid thoracotomy can be performed during the cooling if needed. It can be carried out on the operating table and even instituted in a modified form during operation should the occasion arise. Its main hazard is the possibility of producing tissue damage, especially if

salt has been added to the ice. One of the authors has seen a patient in whom it was decided to induce hypothermia during operation to minimize sequelae resulting from an unforeseen period of partial occlusion of the cerebral circulation. Ice bags were obtained in a hurry and placed blindly under the towels on the patient. The exigencies of the situation did not permit as frequent movement of these bags as would have been desired, and at the end of the operation the patient had a pale area of skin in one groin. Necrosis of this skin occurred over the next few days, but fortunately healing subsequently took place without the necessity for skin grafting. It was found later that the ice was prepared from salt water and the temperature of one of the bags was under 0°C.

Both the above techniques require the wetting of the skin. Unless this is properly dried when the active cooling is stopped the continued fall in body temperature will be greater than one would expect under these circumstances.

Refrigerated blankets. The use of special blankets through which water or other cooling fluid can be circulated enabled Fay to induce hypothermia in 1940. Many workers now favour the method because of the greater control over cooling and ability to switch to reheating if needed (Scurr, 1954; Inglis, Biffen and D'Abreu, 1954; Lewis, Ring and Alden, 1956; Julian et al., 1956; Fairley, 1957). This is particularly important in infants and young children (Scurr, 1955). Despite the fact that cooling is effected by circulating water or other fluid at 4–10°C, cooling is slower than by the other methods already described because the cooling surface in direct contact with the patient is small.

Most forms of blankets used in hypothermia are expensive. Those which incorporate a special refrigerated solution (in place of water) take considerable time to reach the desired temperature and this applies to changes in temperature during rewarming. However, they avoid direct contact of both the patient and attendants with iced water and can be used on the operating table.

Air cooling. The circulation of cold air around the patient as a means of inducing hypothermia has been described Bailey et al. (1954), Adams-Ray, Halberg and Hjelmstrom (1955), Lundberg and Nielsen (1955), and in this country by Forrester (1958). The patient is placed in a cabinet through which air at a temperature of −5°C to −10°C is circulated by a fan. Bailey et al. (1954) abandoned the method because they considered that the extreme coldness of the circulating air carries a risk of frostbite, although this possibility does not seem to have worried other workers. In the apparatus described by Forrester (1958) the air in the cabinet is thermostatically controlled at −5°C for cooling, and air at 40°C is circulated for rewarming. He claims that the method is simple and reliable and although it achieves cooling at a somewhat slower rate than crushed ice, this is counteracted by the increased safety from more direct control of the environmental temperature. All types of apparatus for surface cooling are cumbersome and expensive.

General considerations.

Induction of hypothermia by any method of surface cooling proceeds at a variable rate depending on the technique, the efficacy of the drugs used to suppress shivering and promote vasoconstriction and on the obesity and age of the patient. The temperature continues to fall for a time after removal of the cooling agent. The only study relating the degree of "after-drop" in temperature to the physical state of the patient is that of Burrows et al. (1956) whose records, unfortunately, were confined to the rectal temperature. Using this as a criterion, obese patients cool slowly and have a marked "after-drop", whereas thin subjects cool rapidly and there is little "after-drop". Infants, who have a poorly developed thermo-regulating mechanism, cool rapidly and their temperature continues to fall, often at an alarming rate, for some time. Despite the criticisms which have already been made of the unreliability of the rectal temperature to indicate the temperature of vital organs, these changes are what one would expect on consideration of the temperature gradients associated with the production of hypothermia by surface cooling. By placing the patient between warm blankets (40°C) when active immersion hypothermia was discontinued Sellick (1957) found that the temperature reached its minimum in 25 minutes in children and in 40 minutes in adults, the "after-drop" varying from 1.5° to 2°C.

Many workers consider that the variable con-

tinued drop in temperature is a major drawback to surface cooling. Gray (1955), however, suggests that if the physical build of the patient is taken into consideration the degree of "after-drop" can be predicted with reasonable accuracy. In his large series and those of Vandewater et al. (1958), and of Sedzimir and Dundee (1958), where this technique was used, there were no reported instances of too deep a degree of hypothermia. Virtue (1955) recommends that active cooling should be stopped when two-thirds of the anticipated fall in temperature has been achieved. Burrows et al. (1956) recommend frequent changes in posture to aid redistribution of cooled blood and minimize "after-drop".

The pattern of fall in temperature with the various methods described varies little and the rate at which it changes is the only major difference between the techniques. There is always an interval, which varies from 5 to 15 minutes depending on the technique, before the temperature starts to fall. With immersion hypothermia the rate thereafter is about 1°C every 6 minutes (Sellick, 1957) and about 1°C every 10–15 minutes when ice-packs are used. With the latter method the average time for induction of anaesthesia, cooling, drying, placing on the operating table and towelling up for 174 neurosurgical patients was 122 minutes (Sedzimir and Dundee, 1958), and in these patients this was almost compensated for by a decrease in operating time. In other types of surgery, one must consider the additional time required for the production of hypothermia in relation to the increased safety of the patient, or even the ability to perform the desired operation.

EXTRACORPOREAL COOLING OF THE BLOOD STREAM

The induction of hypothermia by direct cooling of the blood stream was developed independently by Boerema et al. (1951) and Delorme (1952). According to Delorme, cooling by this method obviated the intense body reaction to cold evoked by surface cooling. This is due to the rapidity with which the temperature of the body core is reduced, thus depressing endocrine and hypothalmic activity almost at once. Reflex peripheral vasoconstriction of skin vessels, due to contact with a cold stimulus, and shivering due to temperature gradients are largely avoided by the technique.

These early workers evolved a technique of arterio-venous cooling. Delorme (1952) cannulated the femoral artery and circulated blood through a cooling coil, returning the cooled blood to the femoral vein. Arterio-venous cooling was shown by Ross (1954) and Brock (1956) to have several major disadvantages.

(1) The work of circulating blood through the cooling coil imposes an extra load on the heart at a time when its efficiency is reduced by cooling.
(2) The arterio-venous shunt causes a small, but significant, drop in diastolic pressure; in the case of congenital heart disease this is likely to lead to the shunting of blood from the right to the left side of the heart.
(3) As cooling proceeds the cardiac output falls and consequently the efficiency of the cooling coil is diminished.
(4) The method involves the cannulation of a major artery, with the risk of subsequent thrombosis. Ross (1954) reports this complication in at least two patients despite careful excision of the damaged ends and suture of the artery.

A technique of venous-venous cooling which surmounted these difficulties was developed by Ross (1954). He cannulated the superior vena cava via the external jugular vein in the neck and circulated the blood, by means of a pump through a cooling coil, returning it to the femoral vein via a cannula introduced through the saphenous vein. Brock (1956) has simplified the method further. He inserted both cannulae through the right auricular appendix, passing the outflow cannula into the superior vena cava, and the inflow into the inferior vena cava. Using a Martin pump, blood is circulated through 12 feet of polyvinyl plastic tubing. (Capacity 60 ml.) This tubing is siliconized to minimize platelet destruction and refrigerated by a jacket through which the cooling solution is constantly circulated. The temperature of this cooling fluid is around −5°C. The increase in coagulation time which accompanies cooling of the blood obviates the need for anticoagulants.

A much simpler apparatus, described by Lucas (1956) immerses the cooling coil in a 3-lb.

"Kilner" jar containing a mixture of carbon dioxide snow, saline and alcohol. The amount of alcohol in the mixture determines its temperature; 10 per cent alcohol is commonly used, giving it a temperature of −4°C. The rate of cooling is governed by the rate of circulation of blood through the cooling medium. If cooling is too rapid the temperature of the heart falls too quickly and dangerous arrrhythmias may be precipitated. On the other hand, destruction of platelets and haemolysis, which is a major hazard of extracorporeal circulation, are greater the more the blood circulates through the machine. Brock (1956) considers that maximum safety is achieved with a cooling rate of 1°C every 5 minutes. At this rate a large adult can be cooled to 28°C in 40–60 minutes.

The problems of continued fall in temperature which have been discussed in relation to surface cooling are obviously not applicable to the extracorporeal method. Without any doubt, it is the method which affords the greatest control of the temperature of the vital centres. Cooling is not begun until the thoracotomy has been performed, the diagnosis confirmed and the need for hypothermia indicated. Cooling is carried out with the chest open and the heart is kept under observation, so that there is no delay in resuscitation should ventricular fibrillation occur. Cooling and rewarming can both be carried out more quickly than by any other method. However, the technique is much more complicated than surface cooling; its application is simplest when the chest is already open for cardiac surgery. There is greater interference with clotting and some haemolysis always occurs. Its use is limited to certain cardiac surgery centres and it does not enjoy the overall popularity of surface cooling methods.

With the time limit which hypothermia imposes on open heart surgery and the danger of ventricular fibrillation associated with the hypothermic state, it was not surprising that alternative methods were sought to allow safe circulatory occlusion. These all bear some similarity to the extracorporeal method. Blood is pumped from the venous inflow to the heart, through some type of pump oxygenator and back to the aortic outflow. Melrose (1958) describes the use of cardiorespiratory pumps and readers are referred to his review for further details of the technique In some centres, this form of extracorpore circulation has been combined with hypotherm

Sealy et al. (1957) and Sealy, Brown a Young (1958 a, b) have described a combinati of hypothermia and extracorporeal circulatio for open heart surgery. In their first fifty patient they produced hypothermia by surface cooling However, they were not satisfied with the con trol of temperature which could be achieved by this technique and they explored the extra corporeal method, the experimental results of which had been described by Gollan, Blos and Shuman (1952), Gollan, Hamilton and Meneely (1954), and Pierce and Polley (1953).

The technique was improved by the use of a simple blood heat exchanger (Brown, Smith and Emmons, 1958). The heat exchanger assembly consisted of an automatic thermostatically-controlled water mixing valve (blending hot and cold tap water), heat exchange unit and bubble trap filter. The assembly unit can be used with any extracorporeal circuit and is interposed in the inflow line between the heart-lung machine and the patient's artery. In man, Brown et al. (1958) claim that they can lower the temperature from 37° to 30°C in a few minutes and maintain it evenly at a chosen temperature level to within 0.5°C. Rewarming from 30° to 35°C has been accomplished at only slightly slower rates than that of cooling.

Body cavity cooling. Khalil and MacKeith (1954) introduced intragastric cooling as a means of inducing generalized hypothermia. The method consisted of placing a balloon into the stomach and filling it with 250 ml water at 4°C. The balloon was frequently emptied and refilled with iced water as heat exchange occurred with the circulation. This simple apparatus was successfully used in a hyperpyrexial child. Khalil (1958) further refined the method by using an apparatus to maintain a constant circulation of water at 5°C through the intragastric balloon. A suction pump on the outflow tube displaces a similar volume of water through the inflow tube from a hermetically sealed reservoir, thus ensuring a constant volume of water in the balloon and avoiding the risk of over-distension of the stomach. A thermostat keeps the temperature of the water constant a

5–7°C and a flowmeter is incorporated to maintain a flow of 750 ml per minute. The temperature of the circulating water can be altered quickly, and water at 35–40°C employed to effect rapid rewarming. He reports the successful use of the method during two neurosurgical operations. Barnard (1956) has also described an apparatus and technique for intragastric cooling.

Intragastric cooling has the advantage of controllability and, as with other methods of direct bloodstream cooling, avoids the undesirable tissue gradients between surface and body core which are a feature of surface cooling. Also tissues with a high metabolic rate, particularly the liver, are cooled quickly, giving them a high degree of protection early in the cooling process. These advantages are offset by the extremely slow rate of cooling (an adult required 4 hours to cool from 36.8° to 26°C). Of a more serious nature are extrasystoles which are common during cooling especially in the early stages. Oesophageal temperature readings are no indication of the body core temperature during intragastric cooling.

Blades and Pierpoint (1954) induced hypothermia by perfusing the open thoracic cavity with saline at a temperature of 1–3°C. The large vascular bed of the lung, aorta and pleura are thus exposed to the cooling agent. In dogs so cooled the temperature fell about 1°C every 5 minutes. In one patient in whom the technique was used induction of hypothermia was slow (155 minutes to 30°C) and required a total of 75 litres of saline. Cardiac irregularities were common due to the rapid direct cooling of the heart, and cooling had to be suspended on nine occasions because of electrocardiographic evidence of developing myocardial anoxia. Rewarming is carried out by substituting warm saline and is achieved in half to two-thirds of the time required to effect cooling.

Induction of hypothermia by perfusion of the thoracic cavity is not very practical owing to the large volume of fluid required and the high incidence of cardiac arrhythmias. Rapid rewarming of the heart by perfusing the thoracic cavity with warm saline is, however, a useful resuscitative measure in ventricular fibrillation.

SELECTIVE COOLING OF ORGANS

Each of the methods of producing hypothermia has been modified by various workers to effect local cooling of an organ or organs. In some instances the result has been to produce a localized greater degree of fall in temperature relative to the rest of the body. As will be seen in a later section, selective cooling of organs does not nearly enjoy the popularity of generalized hypothermia.

Refrigeration of limbs. This was popularized by Allen (1938) who observed that reduction in temperature prolonged the survival time of anoxaemic limbs, resulting from vascular occlusion or trauma. Local refrigeration has been used for painless amputation of legs in poor risk patients (Crossman et al., 1942; Helliwell, 1950). The technique employed is a simple adaptation of surface cooling, the bandaged limb being immersed, beyond a tourniquet, until the temperature of deep tissues has been reduced to about 5°C.

Selective brain cooling. Parkins, Jensen and Vars (1954) consider that "the cooling method of choice would seem to be one which afforded the central nervous system adequate protection from anoxia but one which did not increase myocardial irritability". They used selective brain cooling in dogs to produce a brain temperature of 20°C, at which level the rectal temperature was only 32°C. So protected, the dogs withstood cardiac inflow occlusion for 30 minutes without cerebral or myocardial damage. Animals in which brain temperature was reduced below 12°C all showed gross brain damage. At temperatures of 12–18°C, there was no cerebral damage. This selective cooling was effected by diverting the carotid artery flow through a cooling coil of 100 ml capacity, immersed in an ice bath.

Kimoto, Sugie and Asano (1956) further developed the technique and applied it successfully to eleven patients undergoing cardiac surgery. They consider the method to be vastly superior to generalized hypothermia. The carotid artery is cannulated, directing the blood through a cooling coil and by means of a pump returning the cooled blood to the distal side of the carotid artery. Using the internal jugular blood temperature as a guide to brain temperature, cooling was induced to 14°C, and at this temperature the general body temperature was not below 31°C. In experiments on dogs, these workers had

previously noted no significant difference in the temperature of the irrigated and nonirrigated sides of the brain. At the end of operation, when cardiac inflow is restarted and carotid continuity re-established, the brain temperature quickly approximates to the general body temperature.

Selective brain cooling has not received the attention it would appear to merit. Gray (1958) has suggested the danger of carotid artery thrombosis following the technique, although Kimoto, Sugie and Asano (1956) have not experienced this complication in their series.

Klikov (1957) has described a method for local cooling of the brain by means of a blanket, in which ice-cold water circulates, placed on the external surface of the head. In small laboratory animals it was possible to reduce deep brain temperature to 18–20°C, while the general body temperature was only lowered to 30°C. The clinical application of this method of cooling is not apparent, save in the possible treatment of cerebral neoplasms.

Localized brain refrigeration. Rowbotham, Haigh and Leslie (1959) have described a cooling cannula for use in the treatment of cerebral neoplasms. In this is circulated 95 per cent alcohol, which freezes at −110°C. This fluid has been cooled by pumping through a mixture of solid carbon dioxide and acetone, which gives a temperature of −20°C at the tip of the cannula. Brain tissue is such a poor conductor that 2–3 mm from the tip of the cannula it remains at 30°C and the local effect limited to a cylinder of a few millimetres radius. Body temperature is not appreciably affected by this procedure.

Selective cooling of the liver and viscera. Burch et al. (1954) selectively cooled the liver in dogs by placing cooling coils around this organ. Animals so cooled survived occlusion of the aorta for 60 minutes. Parkins, Ben and Vars (1955) reported that generalized hypothermia, although highly effective in preventing paraplegia during aortic occlusion, did not reduce the associated shock syndrome and mortality. Experiments on dogs demonstrated that when combined with hypothermia, selective visceral cooling—just before aortic occlusion—reduced mortality considerably. Selective visceral cooling *per se* is not sufficient to prevent cord damage and general hypothermia is necessary as well.

Huggins and Carter (1957) and Huggins, Carter and McDermott (1957) have studied the feasibility of performing partial hepatectomy using intraperitoneal saline at 2–10°C and achieving liver and intestinal temperatures of about 25°C, while the oesophageal remained at 30–32°C. In animals it was possible to occlude the aorta above the coeliac axis and the portal vein at the porta hepatis while 15 to 90 per cent of the liver was excised. This technique has only been applied to one patient, the hepatic artery being clamped for 53 minutes and the portal vein for 62 minutes. The patient did well for one week after operation, but then died from a staphylococcal septicaemia, autopsy revealing an area of infarction in the right lobe of the liver. This necrosis was attributed to occlusion of the hepatic artery. Bernhard, McMurray and Curtis (1955) found that hypothermia *per se* had no deleterious effects on liver function; therefore, further attention should be paid to the technical details of selective liver cooling.

REWARMING AFTER HYPOTHERMIA

Two of the methods already described for induction of hypothermia, namely extracorporeal and body cavity cooling, can be employed to effect active rewarming by simply replacing the cooling fluid with water or saline at 35–40°C. Methods employing surface cooling offer no such facility and the hypothermic patient must either be allowed to rewarm slowly or be actively rewarmed. Active rewarming is not without danger and there is a risk of causing burns. If chlorpromazine has been used to suppress shivering during the rewarming period, or if its effect has persisted from the cooling period, overheating and the production of hyperpyrexia is possible. Short-wave diathermy has been used to rewarm the hypothermic patient by Blair, Swan and Virtue (1956), but the risk of burning the patient is no less with this method. Werner, Dawson and Hartenberg (1956) have shown that hypothermic dogs will slowly rewarm without evidence of shivering in a room at 24°C, suggesting that factors other than shivering play a significant part in the rewarming process. Most workers prefer to allow the hypothermic patient to rewarm slowly, giving chlorpromazine or analgesic drugs to suppress shivering, and perhaps applying

gentle heat by means of hot water bottles outside the blankets. Normal temperatures are regained in about 6 hours and the method is safe and simple to carry out. The patient should not be returned to the ward before reheating has occurred to around 30°C and is proceeding satisfactorily.

COMPLICATIONS OF HYPOTHERMIA

It is not proposed to discuss the hypothermic state in detail but rather to concentrate on those complications which affect either the methods of inducing hypothermia or its applications in man.

Subcutaneous fat necrosis. This has already been described in relation to surface cooling, and the dangers of using salt in preparing ice for cooling have been emphasized. Subcutaneous fat necrosis was described as a complication of hypothermia in children by Hockinger (1902), and more recently by Collins, Stahlman and Scott (1953), who have quoted several instances. Horvath and Spurr (1956) suggest that this tendency to fat necrosis may be dependent on the chemical composition of infant fat. There is a higher melting point and higher iodine content than in adult fat, and cooling of these layers to below solidification point may lead to necrosis. It is also of interest to note that the fat of hibernating animals has a very low melting point and remains fluid at low body temperatures.

Coagulation defects. Impaired coagulation as a serious complication of hypothermia has been emphasized by Helmsworth, Stiles and Elstun (1955) but denied by Couves, Overton and Eaton (1955). Ellis, Kleinsasser and Speer (1957) and Willson, Miller and Eliot (1958) studied this problem in animals and found a variety of changes in the hypothermic state. These included a decrease in procellerin, proconvertin, prothrombin, fibrinogen platelet thromboplastic factor and circulating platelets, all of which returned towards normal or even exceeded normal, during the rewarming phase. Fisher, Fedor and Lee (1958) have shown that the changes become more marked as the duration of hypothermia is prolonged. Many of the reported changes could be explained by intravascular clotting or intravascular agglutination of erythrocytes, both of which predispose to embolic phenomena. Bunker and Goldstein (1958), who have studied this subject extensively in man, found changes different from those reported in dogs, the one significant finding being a decrease in prothrombin composition.

Decreased blood coagulation obviates the need for anticoagulant therapy when the extracorporeal method of hypothermia is used. Intractable haemorrhage has not been a serious complication in patients cooled by the surface method, but Dundee et al. (1953a) have reported it as the cause of a fatal outcome in patients with liver cirrhosis. This suggests that while the coagulation changes are not of great importance in patients with a normal clotting mechanism, where this is already affected, as in the case of liver cirrhosis, hypothermia may have more marked effects. Although one cannot draw definite conclusions from a few patients, it is worth noting that Gray (1955) reported what was considered to be a high incidence of pulmonary embolism after hypothermia. This may be due to the factors mentioned previously.

Cardiac effects. Without large doses of vasodilator drugs during the induction of hypothermia, the falls in blood pressure are usually not very serious above 28°C, but below this the fall may be precipitous. Occasionally the degree of bradycardia during hypothermia may be very marked and Cookson and di Palma (1955) have shown that it does not respond to the intravenous injection of atropine.

The most serious hazard of hypothermia is the occurrence of ventricular fibrillation. The limit which this places on the safe lower level of hypothermia has already been mentioned. It is not proposed to discuss the aetiological factors in the production of ventricular fibrillation, except so far as these are relating to the prevention and treatment of this condition. This subject has been discussed fully by Badeer (1958) and Gray (1958). The conclusions of Badeer's review aptly summarize the present state of our knowledge:

"Ventricular fibrillation in hypothermia with and without cardiac surgery is not due to the operation of any one factor. The tendency for the development of accelerating discharges from ectopic centres in the ventricles, coupled with prolongation and variation in the relative refractory period, produced by the lowered temperature, seem to be the most important factors initiating

ventricular fibrillation. Conditions that favour ventricular ectopic discharges such as changes in blood pH, disturbed myocardial Ca–K balance, mechanical stimuli, increased activity of cardiac sympathetic nerves, increased amounts of circulating catechol amines, interference with coronary arterial flow, anaesthetics and drugs, etc., favour the onset of ventricular fibrillation during hypothermia. It appears that prolongation of the refractory period due to cold *per se* and differences in the refractory period due to temperature gradients pave the way for ventricular fibrillation."

This is reminiscent of the numerous aetiological factors suggested as causes of convulsions during anaesthesia. Equally numerous are the suggested forms of therapy, and at one time the same applied to the prevention and treatment of convulsions. In this case the treatment has now been rationalized so as to avoid known aetiological factors, and the prophylactic or therapeutic use of drugs which raise the convulsive threshold. A similar simplified scheme may be adapted to ventricular fibrillation, but until our knowledge allows such an approach, it is necessary to review briefly the many forms of therapy described in the literature.

Animal experiments have shown that pentobarbitone anaesthesia carries a greater risk of ventricular fibrillation than the use of either ether or thiopentone (Covino, Charleson and D'Arnato, 1954; Riley, Barila and Hughes, 1956). These observations have no clinical application in present-day methods of inducing hypothermia. More important are respiratory patterns during anaesthesia. Brown and Miller (1952) have shown that ventricular fibrillation can follow a rapid fall in alveolar carbon dioxide concentration in normothermic dogs, and Swan et al. (1953) suggest that ventricular fibrillation in hypothermic dogs may be initiated by a sudden rise in blood pH from abnormally low levels. These observations link up with the work of Sealy, Young and Harris (1954) who incriminated a rise in serum potassium during hypercarbia as a cause of ventricular arrhythmias, and observed that the hyperkalaemia was most marked in the post-hypercapnoeic period. It might be significant to note that Elliott and Crismon (1947) found that the hypothermic heart was more sensitive to potassium than the normothermic, and that Smith (1956) found an increase in serum potassium levels during hypothermia, although this finding has not been confirmed by other workers (Osborn, 1953; Fleming, 1954; Deterling et al., 1955). However, studies with the heart-lung preparation suggest that alkalaemia does not play any roll in precipitation or preventing ventricular fibrillation in profound hypothermia (Badeer, 1955), while Moulder et al. (1956) noted that alkalosis is associated with a considerable incidence of ventricular fibrillation in hypothermic dogs.

It would appear that anaesthetists should avoid sudden changes in respiration which will affect the pH of blood. Most workers recommend hyperventilation where muscle relaxants have been used, and Severinghaus, Stupfel and Bradley (1957) suggest that the chances of producing gross respiratory alkalosis are no greater during hypothermia than at normal temperatures. Their work shows that increases in carbon dioxide solubility and changes in lung perfusion very nearly balance the decreased production of carbon dioxide. The pCO_2 in hypothermia can be maintained at normal levels for that temperature by ventilating with the same tidal volume and respiratory rate needed to maintain the pCO_2 at 40 mm Hg at normal temperatures.

Myocardial hypoxia has also been postulated as a cause of ventricular fibrillation and the anaesthetic technique employed must not allow any degree of hypoxaemia. Cooling of the blood displaces the haemoglobin dissociation curve to the left, thus hindering the release of oxygen in systemic capillaries. However, Penrod (1951) and Hegnauer, D'Amato and Flynn (1951) found that, in the presence of adequate arterial oxygen saturation, coronary A–V difference remains unchanged at temperatures as low as 17–20°C. This casts doubt on the wisdom of the recommendation of Bigelow et al. (1950) that hyperventilation should be carried out with 5 per cent carbon dioxide to correct this shift in the oxygen dissociation curve and prevent hypoxia.

One other point worth mentioning in relation to the method of producing hypothermia is the observation of Elliott and Crismon (1947) that there was a marked rise in the serum potassium level of shivering hypothermic rats. The connection between hyperkalaemia and ventricular fibril-

lation has already been mentioned, and one can infer that particular attention should be placed on the complete elimination of shivering during hypothermic techniques for cardiac surgery. However, Zaimis, Cannard and Price (1958) found that a lower muscle temperature reduced the magnitude of tubocurarine neuromuscular block, while enhancing that produced by decamethonium.

The aetiological factors of ventricular fibrillation have been discussed in some detail since they are within the direct control of the anaesthetist. The remaining factors come more directly within the province of the surgeon or his associates.

Mechanical stimulation of the cold heart, as a factor in inducing ventricular fibrillation, has already been mentioned and is supported by the observations of Hegnauer, D'Amato and Flynn (1951) and Reissman and Kapoor (1956). The latter have shown that sudden loading of the right heart after circulatory occlusion is another precipitating factor and they suggest that the clamps be released in stages.

Ito, Faulkner and Koff (1957) and Severinghaus, Stupfel and Bradley (1957) have drawn attention to the metabolic acidosis which occurs after cardiac inflow occlusion. Brewin et al. (1955) point out that the occurrence of ventricular fibrillation when the clamps are released may be associated with flooding of the heart with blood at a low pH. Another factor may be the accumulation of catechol amines and metabolites in the venous blood during occlusion. Berne (1954) has demonstrated that adrenaline can easily induce ventricular fibrillation in the hypothermic heart, and it is interesting to note that Cookson, Neptune and Bailey (1952) found that an adrenolytic drug, benzodioxane, markedly reduced the incidence of ventricular fibrillation following circulatory occlusion.

The role of the cardiac nerves in the production of ventricular fibrillation has been studied by many workers. Radigan, Lombardo and Morrow (1956) demonstrated the prophylactic value of infiltration with procaine at the junction of the right atrium and superior vena cava, while Webb (1956) found that atrioventricular block gave more complete protection. Schumacker et al. (1956) found that bilateral sympathetic block or the use of a sympathetic blocking agent (trimetaphan) were both useful measures in reducing the incidence of ventricular fibrillation. They also found that bilateral cervical vagatomy gave no protection, but stimulation of the undivided right vagus reduced the incidence of fibrillation. Montgomery, Prevedel and Swan (1954) found that neostigmine-induced vagal stimulation was also of value as a prophylactic measure. All these results point to increased sympathetic activity and perhaps decreased vagal tone favouring the onset of ventricular fibrillation. The only clinical application of this to date is the use of acetylcholine, neostigmine or mecholyl to produce bradycardia or even cardiac arrest and protect against ventricular fibrillation. A reduction in oxygen utilization by the arrested heart is also a point in favour of the use of these drugs.

Many drugs have been investigated for their anti-fibrillating activity and Stephenson and Main (1956) and Berman, Taylor and Fisch (1958) have commented favourably on the value of quinidine, especially in conjunction with acetylcholine-induced arrest. Garamella, Hay and Andersen (1956) have described the use of RO 2-5803 while Covino and Hegnauer (1956) were impressed with the value of ambonestyl. The pressor amine, mephentermine has been shown by Covino (1958) to be useful in preventing ventricular fibrillation, while Lombardo, Radigan and Morrow (1957) favour the use of acetylstrophanthin below inflow occlusion to prevent both myocardial failure and diminish the incidence of fibrillation. Angelakos, Torres and Driscole (1958) found that the digitilization *per se* did not affect the incidence of hypothermic ventricular fibrillation, while Radigan, Lombardo and Morrow (1956) found that the intravenous or intrapericardial use of procaine increased its incidence and particularly the mortality.

Mayor, McElroy and Mahoney (1956) demonstrated the value of hypertonic solutions of dextrose in resuscitating the hypothermic heart after ventricular fibrillation had occurred, while Beavers and Covino (1956, 1957) have shown that aminoacetic acid (glycine) is of value. Caranna, Telmosse and Swan (1958), who investigated the merits of the infusion of a number of nutrient solutions, found that dextrose, glycine and fat all possessed a prophylactic antifibrillatory action in the hypothermic dog undergoing right

ventriculotomy. Woodell, Fairley and Bigelow (1957) have shown that heparinized blood is superior to citrate for infusion during hypothermia and reduces the incidence of irreversible ventricular fibrillation.

It is not surprising to find that selective coronary perfusion of warm arterial blood reduced, practically to zero, the incidence of both ventricular fibrillation during cardiac occlusion and cardiac failure on re-establishment of normal circulation (Jude, Fauteux and Haroutunian, 1956). This agrees with the findings of Shumway, Gliedman and Lewis (1955). Coronary perfusion has the added advantage of increasing the safe period of cardiac occlusion during hypothermia.

Following the studies of acetylcholine-induced cardiac arrest by Moulder et al. (1956) and Sergeant, Geoghegan and Law (1956), Brockman and Fonkalsrud (1958) have studied the possibilities of combining hypothermia (28–30°C), mecholyl-induced cardiac arrest and perfusion of coronary vessels with oxygenated blood. This promising technique has not yet been evaluated in man, but it is included here to show how the application of knowledge of some of the aetiological factors can be used to reduce the hazard of ventricular fibrillation.

The management of ventricular fibrillation during hypothermia depends entirely on the circumstances under which it occurs. Cessation of effective cerebral circulation is not as serious an accident when the brain is already protected from hypoxia by the cooling, and the urgency of re-establishing the circulation is not so great. In heart surgery Ross (1957) ignores ventricular fibrillation during the intracardiac part of the operation: by first correcting the cardiac defects the circulation is improved and the chance of effecting successful defibrillation is enhanced. Kay and Gaertner (1956) have shown that the hypothermic heart is more difficult to defibrillate than the normothermic; therefore treatment will have a greater chance of being successful when the heart is rewarmed. Blades and Pierpoint (1954) have effected rapid rewarming by perfusing the open thoracic cavity with saline at 40°C. Ross (1957) could quickly get the bloodstream rewarming under way by using the extracorporeal method. In operations where the thorax is not already opened and where surface cooling has been used, effective cardiac massage can maintain cerebral oxygenation until the temperature of the heart is raised. Fortunately, ventricular fibrillation is not a common complication of these operations.

Before attempting electrical defibrillation the heart should first be massaged to correct myocardial hypoxia and improve tone. If this is not easily achieved, 2–3 ml of 1 : 10,000 adrenaline or 5–10 ml of a 1 per cent solution of calcium chloride should be injected into the left ventricle, and massage continued for a few minutes before attempting defibrillation. The initial electrical shock should be 130 volts for 0.25 seconds. The two dangers of electrical defibrillation are burns of the heart and bubble formation in the coronary vessels (Milstein, 1956). These can be minimized by adequate contact of the electrode with the heart and by keeping the duration of each shock as short as possible, and not longer than 0.5 second. Milstein has also described a chemical method of defibrillation which, although less effective, can be used when an electrical defibrillation apparatus is not available.

A method of closed chest defibrillation has been described by Kouwenhoven et al. (1957) using hand electrodes on the chest wall. The current recommended is 480 volts for adults and 240 volts for children, the shock being maintained for 0.25 second. They have reported the successful application of this to two human patients.

Ventricular fibrillation can last for over 1 hour with subsequent complete recovery of the patient. Husfeldt and Secher (1956) and Martinez, Kass and Hoffman (1958) report durations from 50 to 114 minutes in which normal rhythm was restored after the temperature had been raised above 32°C. The latter workers occlude the aorta above the left subclavian artery to divert the blood flow to the brain and coronary circulation.

Other complications. Henneman, Bunker and Brewster (1958) have pointed out that shivering, occlusion of major vessels and transfusion of citrated blood can lead to a severe metabolic acidosis during recovery from hypothermia. Ludbrook and Wynn (1958) found high plasma citrate levels during the infusion of citrated blood into four patients undergoing surgery under hypo-

thermia. One of these patients died with signs attributable to citrate intoxication. These signs include (*a*) hypotension, which fails to respond to transfusion or vasopressor drugs (*b*) QTc prolongation on the electrocardiogram and (*c*) excessive bleeding from the wound. This condition may therefore be difficult to detect during hypothermia and, while citrated blood should be avoided if possible, if in doubt, the use of a 1 per cent solution of calcium chloride given slowly in doses up to 1 gramme is advised.

CLINICAL APPLICATIONS OF HYPOTHERMIA

From the foregoing discussion, many of the clinical applications of hypothermia will already be apparent. It is now proposed to classify these indications and discuss their present day use.

Neurosurgery.

It is surprising that, five years after the introduction of hypothermia into clinical practice, neurosurgery should be listed first among the indications for the technique. The obvious application for hypothermia is to permit safe circulatory arrest and it would seem to be eminently suitable for cardiac surgery. Unfortunately, as has been mentioned, the problem of ventricular fibrillation in cardiac surgery is by no means solved. Two major factors in its production, viz. handling of the heart and metabolic acidosis after release of clamps following cardiac inflow occlusion, do not apply to neurosurgery. One has only to consider three recent publications to realize the significance of this. The reports of Botterell et al. (1958), Hellings (1958) and Sedzimir and Dundee (1958) concern a total of 409 patients, of which 269 had cerebral aneurysms. The operations were conducted with temperatures around 28–30°C, and ventricular fibrillation only occurred on two occasions, one of which was fatal. Furthermore, these two cases of ventricular fibrillation occurred in the early days of the use of hypothermia (Vandewater, Botterell and Lougheed, 1955) and were probably related to respiratory acidosis, the significance of which was not appreciated at the time (Vandewater et al. 1958).

The rationale for the application of hypothermia to neurosurgery is twofold. Firstly it permits partial or complete occlusion of the cerebral circulation for periods of time which allow accurate repair of a ruptured aneurysm, or treatment of an arteriovenous anomaly to be carried out in a dry field. Although not often needed, vascular occlusion is also sometimes of value in removal of cerebral tumours (Lougheed et al., 1955). The value of hypothermia in preventing cerebral hypoxia has been established by the experimental work of Rosomoff and Holliday (1954), Lougheed and Kahn (1955), Adams et al. (1956), and Bering et al. (1956). It is not surprising to find that these independent teams differ in their opinions as to the degree of protection derived from safe levels of hypothermia, but it is generally agreed that the maximum advantages, with minimum risk, are achieved at temperatures of 28–30°C (Gray, 1958).

Vandewater et al. (1958) report the uneventful occlusion of both common carotid and vertebral arteries for 15 minutes 10 seconds at 26.6°C, both common carotid arteries for 15 minutes at 26.5°C, and one common carotid artery for 16 minutes 30 seconds at 31.4°C, while Sedzimir (1956) found no ill effects after complete occlusion of the middle cerebral artery for periods up to 15 minutes at 29–30°C (Gray, 1955).

The second indication for the use of hypothermia in neurosurgery is best described as "safer hypotension" (Dundee, Francis and Sedzimir, 1954). It is not necessary to elaborate on the advantages of hypotension to the neurosurgeon, especially during removal of vascular tumours or surgery of aneurysms. While Crumpton et al. (1952), Morris et al. (1953) and Stone, Mackerell and Wechsler (1955) have shown that the decrease in cerebrovascular resistance during chemically induced hypotension permits adequate cerebral oxygenation at low blood pressures in normal subjects, Hughes (1955) found evidence of interference with the cerebral circulation in some subjects, and cerebral damage has been demonstrated by the flicker-fusion test (Nilsson, 1953) and by the electroencephalogram (van Bergen et al., 1954) after its use. Any pre-existing interference with cerebral blood flow, as may be present in patients with cerebral tumours or intracranial haemorrhage, will accentuate the effects of hypotension, and cerebral hypoxia may ensue. Aserman (1953) has described "retractor anaemia" as a cause of death in three neurosurgical patients following induced hypotension.

He suggests that pressure by a retractor may be transmitted to comparatively distant parts of the brain, depriving them of their blood supply and causing irreversible and possibly widespread damage. By virtue of its effect in reducing cerebral oxygen consumption, hypothermia should help in protecting the brain from all these adverse effects of induced hypotension.

There is not general agreement as to the time for which hypotension can safely be employed during neurosurgical operations. Hellings (1958) considers it advisable, in cases of brain damage with spasm of the cerebral vessels, to limit the low blood pressure to the shortest possible time. On the other hand, Botterell et al. (1958), while admitting that dissection of an aneurysm and manipulation of the cerebral artery bearing it may cause arterial spasm and traction damage to the perforating vessels, nevertheless, the deleterious effects of spasm may be avoided when the hypothermia outlasts the spasm. Sedzimir and Dundee (1958) consider that the combination of hypothermia and hypotension provides so much better operating conditions that operative trauma and damage to blood vessels is reduced to a minimum; they do not hesitate to use trimetaphan camphorsulphonate (Arfonad) when hypothermia alone does not provide sufficient hypotension. However, the period of profound hypotension is kept as short as possible and limited to the time when the cerebral aneurysm is being handled. Campkin and Inglis (1958) regard hypothermia as an essential part of the anaesthetic technique when controlled hypotension to below 80 mm Hg is adopted and this applies to the majority of vascular cerebral tumours. With increasing use of hypothermia to make hypotension safer this difference of opinion will probably become less marked and, as will be discussed later, the moderate degree of hypotension produced by the reduction in body temperature, and the excellent operating conditions which hypothermia gives, will probably reduce the need for hypotensive drugs.

All these clinical reports, together with those of Dundee and Mesham (1954), Burrows et al. (1956), Lundberg, Nielsen and Nilsson (1956), Inglis and Turner (1957) and Bohm et al. (1957), and the review of Little (1958), refer to the excellent operating conditions provided by hypothermia for intracerebral operations. In addition to reducing cerebral metabolism, Rosomoff and Gilbert (1955) and Adams et al. (1956) have shown that hypothermia decreases cerebrospinal fluid pressure and at 25°C the intracranial space not occupied by the brain is increased by about one-third. Cerebral blood flow and venous pressure are also reduced in proportion to the degree of hypothermia. Obrador, Elio and Anastasio (1954) and Lundberg, Nielsen and Nilsson (1956) found that induced hypotension alone has a slight effect, if any, on the persistent increase in intracranial pressure in the case of brain tumours. Sedzimir and Dundee (1958) reported that, even in the presence of large neoplasms and advanced papilloedema, in the majority of patients the brain did not bulge, the dura was not tense and dissection of tumours did not need the same amount of manipulation and retraction when hypothermia was employed.

Lundberg, Nielsen and Nilsson (1956) are even more enthusiastic about the benefits of hypothermia and suggest that by preventing local hypoxia during operation, the incidence of postoperative cerebral oedema is reduced. The implication of this in the management of patients with cerebral trauma will be discussed later. In operations on the brain stem, postoperative coma and hyperpyrexia are caused, in part at least, by tissue swelling with consequent cellular damage from trauma. Reports from Inglis and Turner (1957) and Campkin and Inglis (1958) suggest that these sequelae to operation have been greatly reduced since the technique of hypothermia has become a routine.

Surface cooling, as outlined, is almost universally adopted for neurosurgery. The means of application of cold does not seem to affect the efficacy of the hypothermia, but there are some particular details of the method of anaesthesia which must be considered. The basic requirements of neurosurgical anaesthesia have been outlined by many writers and Ballantine and Jackson (1954) have emphasized the importance of a perfect airway, complete absence of coughing and straining and the deleterious effects of either a rise in venous pressure or carbon dioxide retention. Deviations from any of these requirements can easily reverse any of the benefits of hypothermia in producing good operating conditions,

and Campkin and Inglis (1958) stress that controlled hypotension is of no avail when bleeding is principally venous. Furthermore, many neurosurgeons prefer to have spontaneous respiration throughout the operation, as alterations in the pattern of respiration can indicate encroachment on vital centres in the mid-brain. Spontaneous respiration is also considered the best method of keeping the venous pressure within normal limits.

The control of shivering is as important during neurosurgery as it is with any other application of hypothermia as, in addition to increasing oxygen consumption, Rosomoff and Gilbert (1955) have shown that it causes a rise in cerebrospinal fluid pressure. This may be why Lemmen and Davis (1958) failed to find a fall in intracranial pressure with hypothermia. Preference for spontaneous respiration throughout the operation precludes the use of long-acting muscle relaxant drugs to control shivering. Nitrous oxide, although a valuable aid to the control of shivering (Parkhouse, 1957), is often not sufficient alone, and large doses of analgesic drugs are precluded because of their depressant action on respiration with the subsequent rise in cerebrospinal fluid pressure. Chlorpromazine is effective in a certain number of patients, but often large doses are required and these can result in severe tachycardia and hypotension which may be difficult to reverse. The use of ether, while very effective in controlling shivering, is limited to a short period after induction of anaesthesia because of its flammability. Although it is too early to comment conclusively on the benefits of halothane as an adjuvant to surface cooling, the reports of Vandewater et al. (1958) and Campkin and Inglis (1958) suggest that in low concentration it is the most suitable drug available for this purpose in neurosurgical anaesthesia.

It is interesting to note that during the induction of hypothermia with spontaneous respiration, Vandewater et al. (1958) did not find any marked alteration in the pH of arterial and venous blood. This confirms the observations of Severinghaus, Stupfel and Bradley (1957) that the increased solubility of carbon dioxide at low temperatures compensates approximately for its decreased production. It is also obvious that, with light anaesthesia, at 28–30°C, spontaneous respiration remains adequate to maintain efficient oxygenation.

Another problem of hypothermia which is peculiar to neurosurgery is the possibility of extending the duration of the reduction in body temperature into the postoperative period. This is frequently desirable after prolonged periods of vascular occlusion, especially where there has been spasm of the vessels, or in patients who have had an intracerebral haemorrhage. Technically this does not cause much trouble for, provided shivering is prevented, if no active steps are taken to rewarm the patient, the temperature may remain at subnormal levels for 12 to 24 hours after operation. However, it is recommended that the temperature should be first raised to 28°C if necessary (Sedzimir and Dundee, 1958). The risks of maintaining patients below this temperature more than outweigh any advantages. Prolonged therapeutic hypothermia will be discussed in more detail later.

If suitable thermocouples are not available for measuring oesophageal temperature, resource may have to be made to rectal temperatures during neurosurgical procedures. The disadvantages of this have already been mentioned and one is again reminded that brain temperature will probably be slightly lower than that recorded in the rectum (Hellings, 1958). Most workers are agreed that the optimum temperature for neurosurgical operations is 28–30°C, although continental workers put this figure slightly lower (Ciocatto and Cattaneo, 1956). Surgery for aneurysms, where prolonged vascular occlusion may be required, is usually carried out in young subjects who, fortunately, tolerate a more marked degree of hypothermia than the more elderly patients who form the bulk of the subjects with tumours. Trimetaphan, when used to reduce the blood pressure, takes longer to act at low temperatures. Variability of responses to the drug is, however, as great during hypothermia as at normal temperatures and most workers have encountered patients with almost complete resistance. In one such patient increasing the infusion rate resulted in apnoea for 15 minutes (Burrows et al., 1956). This possibility must be remembered as a differential diagnosis for the apnoea which can follow carotid occlusion or surgical interference with the mid-brain.

CARDIAC SURGERY

In 1952, Cookson, Neptune and Bailey suggested the use of hypothermia as a means of performing intracardiac surgery under direct vision, and in the following year Swan et al. (1953a) described the physiological changes following circulatory arrest under hypothermia. Bigelow, Mustard and Evans (1954) further clarified the physiological concepts of hypothermia and their applications to cardiac surgery.

Increasing knowledge of underlying principles and an accumulation of clinical data has shown that there are very marked limitations to the application of current hypothermic techniques to cardiac surgery. The principles of these limitations have already been discussed and their clinical significance is as follows:

(1) Safe hypothermia (28–30°C) permits not more than a 10-minute occlusion of cerebral blood flow.

(2) Since the beating hypothermic heart continues to use relatively more oxygen than other tissues at the same temperature, Swan (1956) and Ross (1957) place 8–10 minutes as the upper safe limit of cardiac occlusion. Lombardo, Radigan and Morrow (1957) have shown that this time can be increased to 16–20 minutes by coronary perfusion, but this does not affect cerebral circulation. Gollan and Nelson (1957) have shown that the artificially arrested heart can stand longer periods of hypoxia.

(3) Circulatory occlusion raises the problem of metabolic acidosis due to venous congestion of tissues and accumulated metabolites (Neil, 1957).

(4) The dangers of ventricular fibrillation are ever present during cardiac surgery under hypothermia, and a solution to this problem would open up new fields.

(5) Much remains to be done in assessing the clinical use of procedures which increase the safety of hypothermia, e.g. controlled circulatory arrest, coronary perfusion and a combination of the hypothermic and cardio-respiratory pump techniques.

Large series of cardiac operations performed under hypothermia have been described by Brock (1956), Julian et al. (1956), Swan and Blount (1956), Fairley (1957), Brown et al. (1958), and Swan, Wilkinson and Blount (1958). There is little to be gained from a detailed analysis of each of these individual papers, but from a perusal of their contents the following indications for hypothermia in cardiac surgery become apparent:

(1) Operations on the atria

(*a*) Repair of ostium secundum type of atrial defect. This is by far the most successful application of the hypothermic technique to cardiac surgery. The operation can be done quickly and accurately under direct vision in less than 8 minutes. The ostium primum defect takes about 20 minutes to repair; the hypothermic technique does not provide this time.

(*b*) Excision of tumours of the heart under direct vision. The most common of these is the myxoma of the left atrium which is approached through the right atrium and septum. Successful removal of these tumours under hypothermia has been reported by Chin and Ross (1957) and by Krcilkova et al. (1958), while Bahnson, Spencer and Andrus (1957) prefer a combination of hypothermia and artificial circulation.

(*c*) Tricuspid valvular stenosis. Brock (1956) finds the blind approach unsatisfactory as it is difficult to be certain just where the commisures are. There is usually considerable regurgitation present and the stenosis can be relieved and a plastic repair done under direct vision.

(*d*) Long standing uncompensated mitral stenosis which cannot be improved by medical treatment. There is some controversy about the value of hypothermia in these cases, but Bigelow and Greenwood (1954) report its use in four very ill patients with good results.

(2) Operations on the ventricles

(*a*) Pure pulmonary infundibular stenosis. This requires an open operation to avoid damage to the tricuspid valve. Brock (1956) reports open infundibular resection and pulmonary valvotomy in three patients with Fallot's tetrology performed under hypothermia.

(*b*) Ventricular septal defects. The hypothermic technique is unsuitable for repair of this anomaly and Brock (1956) advises the use of a pump-oxygenator.

(3) Relief of pulmonary or aortic valvular stenosis. This can be carried out via the great vessels, the operating time being only 4–5 minutes which is safe at 30°C. The first successful direct-vision operations on the aortic valve were reported by Swan and Kortz (1956) and Lewis et al. (1956). Swan, Wilkinson and Blount (1958) have recently reported the use of hypothermia in eleven such patients, but Lillehei et al. (1956) prefer general body perfusion methods with retrograde perfusion of the coronary sinus, claiming that it provides a somewhat safer operating time for the procedure.

SURGERY OF THE GREAT VESSELS

Surgery requiring occlusion of the aorta carries with it the risk of damage to the spinal cord, kidneys, liver and viscera. Occlusion of the thoracic aorta necessarily cuts off a major part of the blood supply to the spinal cord via the spinal branches of the posterior intercostal arteries. The need to provide hypothermia during such occlusion has been exemplified by Pontius et al. (1954) and Thornton (1957). The former have shown that at normal body temperature the spinal cord can safely withstand occlusion of the thoracic aorta for 20 minutes. Combined with a safe degree of hypothermia this interval is prolonged to 60 minutes. They also point out that the blood supply of the cord is not embarrassed if occlusion is below the origin of the renal arteries. Beall et al. (1956) and Thornton (1957) draw attention to the protection which hypothermia affords the kidneys during surgery of the aorta. The latter emphasizes the necessity of providing such protection if the lesion is 2 cm or more above the origin of the renal arteries. Attention has already been drawn to the work of Parkins, Jensen and Vars (1954) in another section of this review. They report the greater protection which is afforded the liver and viscera by combining generalized hypothermia at 30°C with selective visceral cooling. It is evident from the facts just stated that generalized hypothermia has a wide application in the surgery of aortic aneurysms above the origin of the renal arteries. Hypothermia is, however, unnecessary in the correction of coarctation of the aorta in view of the extensive colateral circulation.

The protection of the brain by hypothermia is essential during operations on the carotid arteries. Rob and Wheeler (1957) have successfully employed hypothermia in twenty-seven patients undergoing surgery for the relief of occlusion of the internal carotid artery.

Miscellaneous surgical procedures. Hypothermia has been widely used during extensive operative procedures and for the poor risk patient (Dundee et al., 1953a; Barclay et al., 1954; Murray, 1955; Albert et al., 1956). The technique offers many advantages to these patients, viz. the metabolic needs are matched to the reduced cardiac and respiratory functions; dosage of general anaesthetic drugs is reduced and the need for analgesic drugs in the postoperative period is minimized (Murray, 1955); the stress response to operation is reduced (MacPhee, Gray and Davis, 1958) although the output of adrenocorticoids is greatly increased during the rewarming period. However, the reduced stress response during the considerable trauma of extensive surgery must greatly reduce the mortality and morbidity of such procedures. Hypotension is also safer during hypothermia and blood loss is minimized.

Barclay et al. (1954) reported favourably on the use of hypothermia in poor risk patients undergoing thoracic surgery. They considered it was possible to increase the operability rate for lung resection in a number of extremely ill patients with carcinoma or tuberculosis who would not have withstood operation by conventional methods.

Murray (1955) used induced hypothermia in extensive pelvic surgery for carcinoma of the cervix, and emphasized the excellent postoperative condition of the patients compared to those having similar operations under spinal or general anaesthesia.

Murray and Bruce (1955) report the successful use of hypothermia in a moribund patient undergoing hysterectomy for postpartum haemorrhage, and emphasize that it is imperative in these circumstances to restore the circulating blood volume as adequately as possible before giving the "lytic cocktail".

Albert et al. (1956) also commented on the excellent postoperative condition and the greatly reduced drug dosage in poor risk patients under-

going a variety of operative procedures under induced hypothermia. The procedures included thyroidectomy, lobectomy, pneumonectomy, radical hysterectomy and various abdominal operations.

All these workers employed moderate degrees of hypothermia down to 30°C and none reported any serious complications attributable to the hypothermic technique.

The greater protection which hypothermia offers to the liver during resection of hepatic tumours, etc., has been emphasized by Bernhard, McMurrey and Curtis (1955) and Bernhard, Cahill and Curtis (1957). Eiseman, Owens and Swan (1956) consider that induced hypothermia has a place in minimizing the hepatotoxic effect of anaesthetic drugs in operations for portocaval anastamosis and in advanced portal cirrhosis. Many workers question the wisdom of employing a technique which causes an increased haemorrhagic tendency in patients with an already embarrassed blood clotting mechanism, and Dundee et al. (1953a) reported a death from intractible haemorrhage in a patient with disturbed liver function in whom hypothermia had been employed.

Joos and Johnson (1958) have used hypothermia as an aid to aortography in infancy and early childhood. The safety of the investigation is increased and the technical quality of the result is improved by reducing cardiac output and arterial blood flow.

THERAPEUTIC MEASURES

There has been an increasing use of hypothermia as a therapeutic measure in various conditions over the past few years. Most of these are medical conditions not requiring operative interference, although surgery which does not require hypothermia may have to be carried out as an adjuvant in treatment.

Much of what will be mentioned in this section could come under the heading of "anti-hyperthermia therapy", rather than true hypothermia. The degree to which the body temperature is reduced to subnormal limits is often minimal, but for the sake of simplicity all conditions where the body temperature is lowered will be discussed together.

Tumours. Fay (1940) introduced induced hypothermia as a therapeutic measure in medical practice because of the regressions in malignant tumours which occurred when the temperature was reduced. This method was much criticized by his colleagues and never achieved widespread popularity. Its use for treatment of malignant growths in the nervous system was first described by Fay and Smith (1941), using temperatures as low as 23.5°C. Rowbotham, Haigh and Leslie (1959) have recently revived interest in this subject using the special cooling cannula already described. It is too early to comment on the clinical applications of this technique.

Neurological conditions. Hypothermia is being increasingly used as a therapeutic measure in traumatic, vascular and infective neurological conditions, both for its specific effect in cerebral oxygen consumption and to counteract hyperpyrexia.

Fay described the application of hypothermia in the case of severe cerebral trauma as long ago as 1945, and this seems to have been forgotten until Sedzimir applied it again in 1956. Hyperpyrexia is a frequent occurrence in these patients, resulting from disturbed function of the heat regulation centre. In addition to counteracting this, hypothermia reduces metabolic requirements while the brain damage undergoes repair. It may also have a specific effect in preventing post-traumatic cerebral oedema, and it certainly should minimize the effects of any ischaemia which the oedema produces.

Lazorthes and Campan (1958) describe the application of surface cooling to forty-seven patients with severe head injuries, using an air cooling technique—the "atmospheric hibernator" of Laborit. Their rate of cooling was extremely slow and a large number of drugs was given before, during and after the period of hypothermia. In many cases they noticed a vast improvement in the patient's condition at temperatures of 30-34°C, but this was not always maintained. On occasions, patients were rousable and even conscious at these low temperatures, but relapsed when their temperature was raised above 34°C. There did not appear to be any selection of patients in their report and over a quarter died during induction of hypothermia. It would seem from their figures that hypothermia offers most hope in those cases where the actual structural

damage to the brain is not too widespread and where most of the symptoms can be ascribed to oedema or concussion.

The most dramatic report to date of the use of hypothermia is that of Rowbotham et al. (1957). Their patient was intermittently cooled for over five months following a severe head injury, and during that time a healthy infant was born.

In the management of these patients, the use of hypothermia must not be allowed to distract from the general principles of the treatment of head injuries as outlined by Maciver et al. (1958). The prolonged immobility and coma increases the likelihood of atelectasis, and such measures as tracheal suction, physiotherapy and even tracheotomy may often save life. This also applies to the prolonged use of hypothermia in any unconscious patient, e.g. cerebral haemorrhage, encephalitis, etc.

Sedzimir, Jacobs and Dundee (1955), Howell, Stratford and Posnikoff (1956) and Wilson (1958) have described the use of prolonged hypothermia in the treatment of massive cerebral haemorrhage. The principles and method of treatment are similar to those adopted in the case of cerebral trauma. Many workers have used it in preoperative preparation. The factors which determine prognosis in head injuries also apply to this group of patients.

The hyperpyrexia of acute encephalitis has been successfully combated by the use of hypothermia (Johnston et al., 1958; Croft and Henson, 1958; Edwards, 1958). Prolonged periods of hypothermia have been used by these workers, with temperatures as low as 30°C, and all were impressed with its value. Steigman (1958) has reported favourably on the use of hypothermia to counteract both the hyperpyrexia and respiratory insufficiency from polioencephalitis. At a temperature of 31.5°C, however, the metabolic depression did not completely compensate for the respiratory insufficiency. Miorner, Haeger and Ryd (1955) and Veghelyi and Nagy (1955) have also described the beneficial effects of hypothermia in hyperpyrexial patients with polioencephalitis. The control of severe hyperthermia secondary to a urinary tract infection in a patient with multiple sclerosis was reported by Jesati (1956). He considered that the use of hypothermia enabled the patient to survive until the antibiotic therapy became effective.

Paediatrics. The anti-pyrexial therapy in paediatric anaesthesia started the present-day interest in the use of hypothermia. Harris and Hutton (1956) again emphasized the danger of heatstroke during anaesthesia in children and report fatalities in which hyperpyrexia may have been a causative factor. Terry (1957) mentions the added strain that this imposes on the infant and advocates the use of a cooling mattress to keep the temperature at slightly subnormal levels during anaesthesia. Brayton and Lewis (1957) endorse this view and carry it a stage further by using active cooling in children with normal temperatures to prevent the development of postoperative hyperpyrexia.

Miller and Marini (1958) suggest the use of hypothermia in asphyxia neonatorum and state that these children should not be actively warmed.

Thyroid crisis. The pre-operative preparation of a patient with severe thyrotoxicosis by hypothermia was first reported by Dundee et al. (1953a). Hunter (1955) has described the use of a moderate degree of hypothermia in the management of a postoperative thyroid crisis. He used surface cooling aided by chlorpromazine and pethidine and the result suggested that this method can save life.

Miscellaneous. Lewis et al. (1956) and Reeves and Lewis (1958) described the production of a mild degree of hypothermia (35–36°C) in critically ill pyrexial patients (above 40°C) all of whom had a hopeless prognosis. Surface cooling was used and shivering prevented by chlorpromazine and phenobarbitone. Their ages ranged from 6 to 84 years and the pyrexia was due to a variety of causes. Over half of these survived, and best results were obtained in the neurological patients.

von Lüttichau (1955) advises the use of hypothermia as a treatment of severe shock. Although using the word "hypothermia" he was employing the French technique of "artificial hibernation", with a fall in temperature of only 1–2°C. This and the liberal use of numerous drugs distract from the value of his report. The place of hypothermia in haemorrhagic shock is not known. While Postel, Reid and Hinton (1957) reported that it improved survival after experimental

haemorrhage, Ferguson et al. (1958) found that the hypothermic dog was unable to stand a more severe haemorrhage than the normothermic control. More work is needed to evaluate the rationale of using hypothermia in this condition.

Experimental work on dogs by Martin, Stone and Cooper (1958) suggests that hypothermia, induced by air cooling, might find a place in the early treatment of burns. This use of hypothermia was first suggested by Elman et al. in 1942, but its application to man has not yet been reported.

SUMMARY

In this paper the clinical aspects of hypothermia in man have been reviewed. Emphasis has been placed on the methods of inducing hypothermia, their relative merits, complications and indications.

Hypothermia has made great strides within the past five years and is now a recognized therapeutic procedure. There are still many undesirable features of the hypothermic state and a solution to the current problems, as outlined, should further increase the scope of the use of hypothermia. The limitations of hypothermia are also being gradually realized and fuller appreciation of these will increase, rather than distract from, the clinical value of this most useful therapeutic weapon.

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THE EVOLUTION OF ANAESTHESIA

BY

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(*Continued from Vol.* 30, *page* 504)

REFRIGERATION ANAESTHESIA

The numbing effect of cold must have been apparent to many people in the distant past. The repeated failure to make use of this simple method of reducing the pain of surgical operations, even after the technique had been published, and the continued cycle of its rediscovery and neglect are perhaps the most powerful among the reasons for believing that, until the opening years of the nineteenth century, the idea of anaesthesia was not only absent from the public mind, but was positively antithetic to it. Appreciation of this fundamental notion is essential to a proper understanding of the evolution of anaesthesia and the development of the idea of humanity in the public conscience.

Bearing this in mind, and considering the danger which necessarily attended the use of unstandardized drugs, such as opium, it would not be surprising that the action of cold was the first anaesthetic agent to be described, nor that the discovery should come from a country remote from the essentially warm climates of the localities where the earliest civilizations flourished.

Yet snow and ice were known to Hippocrates, who, in his *Aphorisms*, recommends their use to check haemorrhage, and he was even aware of the analgesic action of cold, for he writes, "Swellings and pains in the joints, without ulceration, those of a gouty nature, and sprains are generally improved by a copious affusion of cold water, which reduces the swelling, and removes the pain; for a moderate degree of numbness removes pain". Nevertheless, Hippocrates nowhere advocates cold as a surgical anaesthetic, and, even two thousand years later, the great William Harvey, who treated his own gout according to the method described in this Hippocratic aphorism, was equally uninterested in what, to us, seems its obvious application. In this connexion, it is interesting that Francis Adams, himself a surgeon and the learned translator of the works of Hippocrates, writing as late as 1849, comments on this aphorism, "that all the commentators hold that it (cold) acts, not by producing cold, but by rousing the vital heat of the part". Progress was indeed difficult when physiology was obscured by such curious notions.

There is no extant record prior to the year A.D. 1050 of any effective technique of surgical anaesthesia; the majority of the methods which had been described were purely magical in nature, and all would have been completely ineffective. It was about fifteen years before the Norman Conquest that an unknown Anglo-Saxon monk transmitted to writing the leechbook which Gratton and Singer published in 1952, and which they call the *Lacnunga*. As is to be expected at the height of the dark ages, this collection of recipes and invocations is largely superstitious in nature, but the allusion to cold as a surgical anaesthetic is unequivocal. The translation runs thus:

"Again, for eruptive rash. Let him sit in cold water until it be deadened; then draw him up. Then cut four scarifications around the pocks and let drip as long as he will."

As has been stated, this is the first description of a practicable anaesthetic, and it should be no small matter of pride that it was an Anglo-Saxon discovery. If the work of the Venerable Bede (*c.* 673–735), of Alcuin of York (735–804) and of Roger Bacon (*c.* 1214–*c.* 1294) is considered, it can be seen that the earliest stirrings of what was later to become the Renaissance are more intimately associated with England than orthodox historians are usually prepared to admit.

Refrigeration anaesthesia was discovered only to be forgotten, and no further reference is made to it for more than five hundred years. In 1595, Johannes Costaeus (de Costa) published at Venice his *De Igneis Medicinae Praesidiis*, in which there is a short reference to the use of cold water, snow or ice in relieving the pain of surgical incisions (Bk. I, Cap. 31). Severino of Naples, the originator of comparative anatomy, actually employed this technique, which was seen by Thomas Bartholin, the celebrated anatomist and discoverer of Bartholin's glands, when he visited Italy in 1646. Fifteen years later, Bartholin published at Copenhagen his *De Nivis Usu Medico*, in which he devoted almost a whole chapter (Cap. XXII) to Severino's use of snow as an anaesthetic, but it does not appear that he used the method himself. Osler (Bibliotheca Osleriana, 1378h) thought that Bartholin had realized that cold could be used with benefit in vascular disease, but he was undoubtedly misled by the corrupt state of the text, which abounds in misprints. This is a translation of what Bartholin actually wrote:

"Before treating ulcers of the limbs by cauterization, the rubbing-in of snow produces insensitivity. Marco Aurelio Severino, my old teacher and friend, who is the foremost surgeon of our time, taught me this at the University of Naples. As a general rule, he put the snow in a capacious vessel . . . and applied it to the skin. He told us that, *if we were not afraid of gangrene*, we could apply it under narrow, parallel bandages; in a quarter of an hour, the nerves will be numbed, and it will be possible to make an incision at that point without causing pain. The surgeon can employ this method successfully even when opening up the area between the thighs, close to the perineal arch, for lithotomy. . . . When he wishes to concea' the nature of the treatment, in order to make the results seem more astonishing, the aforesaid Severino dyes the snow with ground ultramarine or some other colouring matter."

From this it will be seen that Severino, far from advocating cold in the treatment of vascular disease, actually warned against its use in the case of impending gangrene.

Despite the reputation of such men as Severino and Bartholin, and the popularity of the latter's books, the resurrected art of refrigeration anaesthesia was again forgotten. Perhaps one reason for this was the advocacy of the method for cauterization; the application of a hot iron would quickly dispel the effects of cooling and destroy the analgesia.

Nevertheless, philosophers were already turning their attention to the use of snow for other purposes. In 1626, Francis Bacon, Viscount St. Albans, literally caught his death of cold while experimenting on the preservation of meat with snow. In 1755, William Cullen invented a sort of refrigerator with which he attempted to reduce small animals to a state of suspended animation, and, eleven years later, John Hunter tried, unsuccessfully, a similar experiment on some carp. James Boswell, Johnson's biographer, satirized these experiments in a witty paper, *On the New Freezing Discovery*, which appeared first in the *Publick Advertiser* of 1770, and was reprinted eleven years later in the *London Magazine*. By the 1790s, the use of cold packs and both the internal and external use of cold water began to be favoured in the treatment of febrile disorders. One of the foremost of these "hydrotherapists" was James Currie, whose *Medical Reports* appeared in 1797.

Refrigeration anaesthesia was discovered once more in 1807, when, after the battle of Preuss-Eylau, Napoleon's Surgeon-General, Baron Dominique Jean Larrey, noticed that amputation could be painlessly performed on soldiers who had lain for some time in the snow. Although this observation seems to have had no direct practical results, the possibility of refrigeration anaesthesia was not again forgotten. When the discovery of the anaesthetic action of ether had shown that surgical anaesthesia was a practical reality, refrigeration was again considered and eventually reintroduced. The credit for this must go to James Arnott (1797–1883), physician of Brighton. Between 1848 and 1867, Arnott published a long series of articles on this subject, the first of which was entitled *On Cold as a Means of Producing Local Insensibility*. (See an interesting and informative article by Marcus Bird in *Anaesthesia*, 1949, **4**, 10.)

Arnott, however, did not restrict his advocacy of cold to anaesthesia. In 1852, he published a pamphlet *On the Internal Application of a Very Low Temperature in Asiatic Cholera*, an idea which foreshadowed the therapeutic use of hypo-

thermia. It is to be noted, however, that Arnott applied the cold by making his patients drink considerable quantities of a saline solution, which had been reduced to a temperature of 26°F (−3.3°C), and it is highly probable that his good results were, in part at least, due to the correction of the patient's depleted salt reserves.

In 1866, Benjamin Ward Richardson, the biographer of John Snow, stimulated by Arnott's successes in local anaesthesia, described his well-known spray. Originally intended to be used with a highly volatile hydrocarbon, called rhigolene, the spray soon came to be used with ether, which proved a satisfactory freezing agent. Richardson's ether spray became so popular that the term "freezing" has passed into the English language as a synonym for local anaesthesia.

The introduction of cocaine as a local anaesthetic in 1884 did not lead to the discontinuance of the use of the spray, which still remained popular for the opening of abscesses. The substitution of ethyl chloride for ether occurred when, in 1890, Redard developed the glass container with spring-loaded nozzle still in use for ethyl chloride today. The new agent proved peculiarly successful in dentistry, partly because the Redard spray could be directed with great accuracy, and partly, no doubt, because the patient inevitably inhaled a quantity of the vapour, and thus achieved a substantial degree of general analgesia. As a matter of fact, the accidental production of full general anaesthesia by Carlson of Gothenburg in two dental patients (1894) was one of the steps in the series of events which led to the introduction of ethyl chloride as a general anaesthetic by Lotheissen of Innsbruck in 1896.

With the advances in local anaesthetic drugs and techniques which were made towards the end of the nineteenth century and during the early part of the twentieth, local refrigeration anaesthesia was almost forgotten. However, in 1905, Simpson and Herring at Edinburgh (*J. Physiol.*, **32**, 305) experimented on the chilling of cats, and observed that, when the body temperature had fallen to about 25°C, the animals became insensible.

To move to a less scientific field, it is interesting that the use of cold as a therapeutic agent had spread to the sphere of Indian folk-lore. Gandhi (*Mahatma Gandhi: His Own Story*, ed. C. F. Andrews, London, 1930, p. 292) tells how, during World War I, an itinerant quacksalver treated his patients, including the Mahatma himself, by the application of ice all over the body.

In 1936, Smith and Fay (*J. Amer. med. Ass.*, 1939, **113**, 653) began the combined use of local and general hypothermia for the treatment of cancer. The rectal temperature of their heavily sedated patients was kept as low as 30 to 32°C for up to five days. The cooling was achieved by exposure to a low room temperature.

In 1937, Frederick M. Allen began his work on local refrigeration for limb surgery, his first paper appearing in the *Transactions of the Association of American Physicians* (**52**, 189) in the year. A number of other papers followed, but he did not succeed in arousing much interest until, in April 1942, he read his important paper, *Refrigeration Anesthesia for Limb Operations* before the American Society of Anesthetists, Inc., at New York (*Anesthesiology*, 1943, **4**, 12).

At this point, respect must be paid to those victims of the Nazi concentration camps who suffered and died from experiments in cooling which were conducted by men whose actions have tarnished the history not only of medicine, but of all humanity. The records of those inhuman trials were rightly destroyed, but the memory of them must not be permitted to fade, lest the bestial Hitlerian régime receive in due course as many coats of whitewash as has that of Napoleon.

To return to the field of science, other early workers in the field of refrigeration were Blalock, Alfred and Mason, who reported (*Arch. Surg.*, 1941, **42**, 1054) the beneficial effect of cold in the prevention and treatment of shock, and stated that "hypothermia, by lowering the rate of metabolism, reduces the tissue requirement for oxygen". In April 1942, Bancroft, Fuller and Ruggiero (*Ann. Surg.*, **115**, 621) were also advocating refrigeration for amputation in cases of diabetic gangrene. By the end of that year, such was the interest in the newly revived technique, that thermostatically controlled refrigerators were in use, thus avoiding not only the risk of contamination from dirty ice but also the labour of cracking large quantities of ice.

In 1946, Kanaar (*Curr. Res. Anesth.*, **25**, 177, 228) pointed out the value of prolonged cooling in the treatment of vascular injuries to the limbs.

By that date, animal experiments were being undertaken at numerous centres and, in 1948, Eichna (*Arch. phys. med.*, **29**, 687) and, in the following year, Lange and his co-workers (*Ann. intern. Med.*, **31**, 989) had both reported ventricular fibrillation at low body temperatures.

Surface cooling of the body by means of ice packs was advocated by Bigelow (*Ann. Surg.*, 1950, **132**, 849), while Delorme (*Lancet*, 1952, **2**, 914) introduced extracorporeal cooling by circulating the blood through a refrigerator system. This method was first applied to man in 1953.

It was at this stage that the method of "artificial hibernation", as it was at first called, was introduced by Laborit and Huguenard, who made use of certain phenothiazine derivatives, especially the then newly isolated chlorpromazine, in order to diminish the homeostatic response of patients to shock. Since the drugs employed caused marked peripheral vasodilatation, a fall in body temperature not infrequently occurred, but this was not an integral part of the technique. Indiscriminate use of the term "hibernation" led to some confusion, which was not lessened when the value of chlorpromazine in the production of surface cooling came to be recognized.

The use of phenothiazine derivatives, especially chlorpromazine and promazine, has greatly extended. These drugs are now used frequently in the treatment of mental disorders, as premedication before general anaesthesia, and as sedatives during operations under local anaesthesia, especially in ophthalmic work, where sedation, low intra-ocular tension and blanching of the eye are combined, without loss of the patient's ability to co-operate. These drugs are also useful in the prevention and treatment of vomiting after anaesthesia, in the management of the intractable pain of inoperable cancer, and, because of the depressant effect upon spinal convulsions, in the treatment of tetanus.

The importance of hypothermia in modern anaesthesia derives from the desire of the surgeon to carry out more and more drastic and time-consuming operations on the heart, vascular system and brain. The success which has attended the introduction of the technique in permitting operations of this sort to be performed is an indication of the vast improvements in anaesthesia which have taken place during the past fifteen years, but it is also a success which could not have been achieved without the closest co-operation and mutual faith between the surgeon and the anaesthetist: it is, more than anything else, a sign that the anaesthetist has at last entered into his rightful place in the surgical team.

At the present time, animal experiments are being conducted in various centres on the problem of cooling the living animal to very low temperatures, even below 0°C. If these experiments should result in a technique by which the human body can be safely reduced to a state of true suspended animation, the boundaries of surgery will become virtually limitless. Nevertheless, caution must be exercised in the approach to such a nirvana; and one particular objection is now looming large indeed. During the last ten years, the duration of surgical operations has increased considerably. The technique of refrigeration is also time-consuming. A few years ago, the amount of surgical work, which could be done in a hospital, depended on the number of beds available; today, the number of operating theatres has become the limiting factor. The cost of new operating theatre blocks is great, and the expense of running an increasing number of them with a full complement of highly trained anaesthetists, surgeons and nursing staff may throw an excessive strain, not only on the Welfare State, but on the institutions of countries in which financial support comes directly from the pockets of the patients. Anaesthesia and surgery are approaching a crossroads, and, so far as can be discerned at present, the signposts are inadequate.

Nevertheless, it begins to look as if John Hunter's hopes may one day be realized and that it will be possible to put a man to sleep for a hundred or a thousand years. Perhaps this may solve some of the problems of the conquest of space.

CORRESPONDENCE

HALOTHANE IN DENTAL ANAESTHESIA*

Sir,—I wish to support Dr. Walsh's favourable appraisal of the use of halothane as an adjuvant for nitrous-oxide dental anaesthesia for out-patients (*Brit. J. Anaesth.*, **30**, 578), and add a few observations.

It is in such usage that I find halothane now almost indispensable, despite its expense. Our experience with it for 2,030 dental cases shows it to be advantageous to the patient, surgeon, anaesthetist and nursing staff. Many of these patients were less than five years old and I do not prefer "other agents such as vinyl ether or ethyl chloride" for minor surgery. The intermittent flow machines are notably innaccurate in their volume and concentration controls and it is well to calibrate carefully under working conditions any attached halothane vaporizer. In children I believe 2 per cent halothane is sometimes necessary for induction purposes and with certain provisos is permissible and safe (McGregor, et al., 1958).

In dental anaesthesia the provisions should, I believe include a cautious unhurried induction of the patient in the supine position with a slight head-down tilt with no hypoxia ever allowed and recovery should occur in the semiprone position in a specially prepared room, properly supervised.

It is regrettable that cerebral damage due to position can be envisaged in 500 Britons a year (Bourne, 1957). And it is also regrettable that it should be necessary to say that "at the end of two minutes the oxygen was *usually* increased to about 10 per cent" or that after "more than ten minutes—usually 15, 16 or *even* 17 per cent of oxygen with nitrous oxide" should be considered commendable (Goldman, Cornwall and Lethbridge, 1948).

At this stage of the development of the science of anaesthesia we are obviously neglecting one important field.

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* The editors wish to draw attention to the third paragraph of this letter and emphasize that the use of halothane in the dental chair with the patient upright might be frought with danger.

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The Physiology of Hypothermia, 1956. Edited by Robert D. Dripps. Proceedings of a symposium convened by the Division of Medical Sciences. National Academy of Sciences—National Research Council. Publication No. 451. Washington D.C.

This volume is the result of combining the resources of clinicians and research workers to determine the value of hypothermia in preventing or treating the stress of operations. There are eighty-six authors and discussants. It was hoped to obtain fundamental physiological information to prevent the technique of hypothermia from degenerating into empiricism.

Hypothermia is surveyed under five main parts which include general physiological considerations; effects on specific systems; myocardial irritability; clinical applications and the techniques involved. These subjects are further subdivided and the discussions following the proceedings are skilfully condensed and reported. There are many excellent illustrations. A subject index is lacking; however the contents pages are well documented and should be useful in finding information. There are numerous lists of references. Each main subject has been reviewed and appraised.

No one interested in hypothermia can afford to be without this most important symposium.

R. P. Harbord

Handbook of Respiration, 1958. Edited by D. S. Dittmer, and R. M. Grebe. Published by W. B. Saunders Co., Philadelphia and London. Pp. 403. 52*s.* 6*d.*

This work contains a vast collection of respiratory data which refer to basic physical and chemical considerations, anatomy, lung functions, blood respiratory characteristics, respiratory pigments, the mechanics of breathing, effects of exercise, artificial respiration, effects of various concentrations of inhaled gases, effects of drugs, factors affecting respiration (e.g., deadspace, acidosis and alkalosis). There is a section on the oxygen consumption of animals and of animal tissues and there is information on the survival of animal tissues after circulatory occlusion.

The 214 references in the section on the "direct action of drugs on the bronchi" alone give some idea of the prodigious coverage.

It is a tribute to the collectors that the reader is rarely, if ever, likely to be in doubt about the sources of information from man or different animal species, or even from plants. This is a capital difficulty in many textbooks, particularly those on pharmacology. Here can be found all that is known about respiratory function in many different animals. There is also information on respiration in plants. For the anaesthetist there is an enormous amount of useful data on respiration, but there is relatively little information on the changes in respiration during anaesthesia.

R. P. Harbord

Principles, Problems and Practices of Anaesthesia for Thoracic Surgery (revised second printing). By Henry K. Beecher, M.D. Published by Charles C. Thomas, Springfield, Illinois, U.S.A. Pp. 74. Price 27*s.* 6*d.*

This little book is a reprint of a previous monograph entitled *Anaesthesia for Thoracic Surgery.* The original text remains throughout the first 65 pages. The last chapter is substantially a reprint of the author's paper "A Comparison of Two Systems of Anaesthesia for Thoracic Surgery" published in 1956. In this ether anaesthesia with assisted respiration is contrasted with unconsciousness produced by thiopentone combined with muscular relaxation provided by suxamethonium. With the latter technique a mechanical ventilator was used. This book throws a most useful light on the methods and outlook of the anaesthetists in one of the largest American teaching centres and it should be read by all who wish to understand in their entirety the numerous and important articles on this subject which appear in the transatlantic literature.

A. R. Hunter

A Handbook of Medical Hypnosis (2nd edition). By Gordon Ambrose and George Newbold. Published by Baillière, Tindall & Cox. Pp. 276. Price 27*s.* 6*d.*

It is unfortunate that hypnosis is so dramatic a phenomenon: the inevitable consequence has been for it to be seized upon by cranks, crooks and conjurors, thus turning it into a black sheep in the medical fold—a black sheep with the mark of the beast. Recent reasonably enlightened legislation has done much to render hypnosis respectable, and it is to be hoped that sincere medical men may in future be able to touch mesmerism without being besmeared. This book should prove a very useful guide to those who are tempted to practise this method of therapy. Certainly the authors are sincere, and, if only for that reason, the book deserves to be read. The first three chapters are really excellent, but in the remaining eight the critical reader becomes aware of a naivety, almost a credulosity, which is at times exasperating. Nevertheless, this book ought to be studied by all anaesthetists, if not by all doctors, because it outlines the many ways in which suggestion may further the patient's interests, and also gives a detailed account of the methods by which suggestibility and hypnosis may be induced. Some may be disappointed that the chapter on "Hypnosis in Anaesthesia" is the shortest in the book, but this is probably in line with practical realities.

Books on hypnosis are legion; good books on this subject are almost non-existent: this book stands high in its genre. Probably only those who are particularly squeamish will resent the use of such words as "hypnoidal", "hypnodontics", "epileptics", and "inducting". The authors discuss the dangers of hypnosis, but are not frightened by them. Your reviewer is less sanguine, and doubts the wisdom of creating a population containing many highly suggestible, because frequently hypnotized, people.

The book contains two forewords. It may puzzle many of us to discover what purpose these excrescences on authorship serve; to load a book with two seems to be piling profitless Pelion upon unnecessary Ossa. Otherwise the book is well designed, well printed and tastefully bound. It is recommended.

M. H. Armstrong Davison

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